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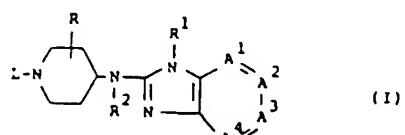
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(54) Bicyclic heterocycl containing N-(bicyclic heterocycl)-4-piperidinamines.

(57) Novel N-heterocycl-4-piperidinamines of the formula



wherein L contains an optionally substituted five- or six-membered ring containing at least one nitrogen atom, and which is condensed with an optionally substituted five- or six-membered ring; the pharmaceutically acceptable acid addition salts and possible stereochemically isomeric forms thereof, which compounds are anti-allergic agents; pharmaceutical compositions containing such compounds as an active ingredient and methods of preparing said compounds and pharmaceutical compositions.

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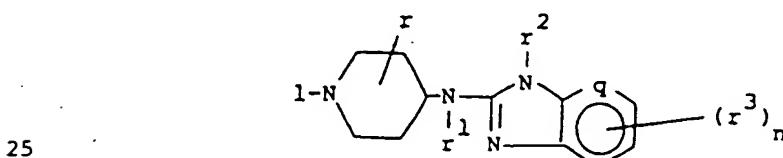
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BICYCLIC HETEROCYCLYL CONTAINING N-(BICYCLIC HETEROCYCLYL)-
4-PIPERIDINAMINES.

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Background of the invention:

In U.S. Patent No. 4,219,559 there are described a number of
20 N-heterocyclyl-4-piperidinamines having the formula



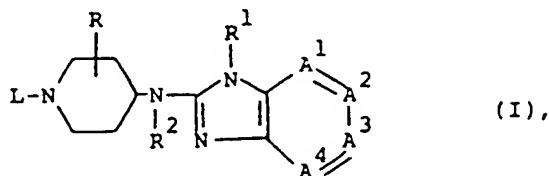
which compounds are useful as antihistaminic agents.

The compounds of the present invention differ from the prior art compounds essentially by the nature of the 1-piperidinyl substituent and by the fact that the compounds of the present invention are not
30 only potent histamine-antagonists but also potent serotonin-antagonists.

Description of the preferred embodiments:

This invention is concerned with novel N-heterocyclyl-4-piperidinamines which may structurally be represented by the formula

5



the pharmaceutically acceptable acid addition salts and the possible
10 stereochemically isomeric forms thereof, wherein:

$A^1 = A^2 = A^3 = A^4$ is a bivalent radical having the formula

15

$-CH=CH-CH=CH-$ (a),

$-N=CH-CH=CH-$ (b),

$-CH=N-CH=CH-$ (c),

$-CH=CH-N=CH-$ (d), or

$-CH=CH-CH=N-$ (e),

wherein one or two hydrogen atoms in said radicals (a) - (e) may, each independently from each other, be replaced by halo, lower alkyl, lower alkyloxy, trifluoromethyl or hydroxy;

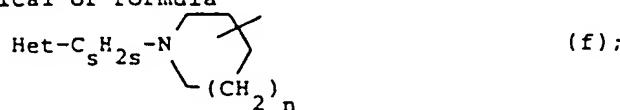
20 R is a member selected from the group consisting of hydrogen and lower alkyl;

R^1 is a member selected from the group consisting of hydrogen, alkyl, cycloalkyl, Ar^1 and lower alkyl substituted with one or two Ar^1 radicals;

25 R^2 is a member selected from the group consisting of hydrogen, lower alkyl, cycloalkyl, (lower alkyl)-CO-, lower alkyl-O-(CO)- and Ar^2 -lower alkyl;

L is a member selected from the group consisting of
a radical of formula

30



a radical of formula



a radical of formula



wherein n is 0 or the integer 1 or 2;

s is 0 or an integer from 1 to 6 inclusive;

5 Alk is lower alkanediyl;

Y is O, S, NR³ or a direct bond;

X is O, S, CH-NO₂ or NR⁴;

Z is O, S, NR⁵ or a direct bond; and

Het is an optionally substituted five- or six-membered heterocyclic
10 ring containing at least one nitrogen atom and being condensed with an
optionally substituted five- or six-membered ring,
provided that:

15 i) when Het is connected to C_sH_{2s} on a carbon atom then
said five- or six-membered ring is not condensed with an
optionally substituted benzene ring;

ii) when L is a radical either of formula (f), or of formula
(g) wherein Y is other than a direct bond, or of formula
(h) wherein Z is other than a direct bond, wherein in said
radicals (f), (g) or (h) Het is connected to C_sH_{2s} on

20 a nitrogen atom then s is not 0;

iii) when A¹=A²-A³=A⁴ is a radical of formula (a) or
(b) and L is a radical of formula (g) wherein s is 0 and
Y is a direct bond then Het is other than a 2,3-dihydro-
2-oxo-1H-benzimidazol-1-yl or a 2,3-dihydro-3-oxo-
25 benzoxazin-4-yl radical;

30 said R³ being hydrogen, lower alkyl, (Ar²)lower alkyl, 2-lower
alkyloxy-1,2-dioxoethyl or a radical of formula -C(=X)-R⁶, R⁶
being hydrogen, lower alkyl, Ar², Ar²-lower alkyl, lower alkyloxy,
Ar²-lower alkyloxy, mono- or di(lower alkyl)amino, Ar²-amino,
Ar²-lower alkylamino or Ar²-lower alkyl(lower alkyl)amino;

35 said R⁴ being hydrogen, lower alkyl, cyano, nitro, Ar²-sulfonyl,
lower alkylsulfonyl, lower alkylcarbonyl or Ar²-carbonyl; and

40 said R⁵ being hydrogen or lower alkyl;
wherein Ar¹ is a member selected from the group consisting of
phenyl, being optionally substituted with up to three substituents each

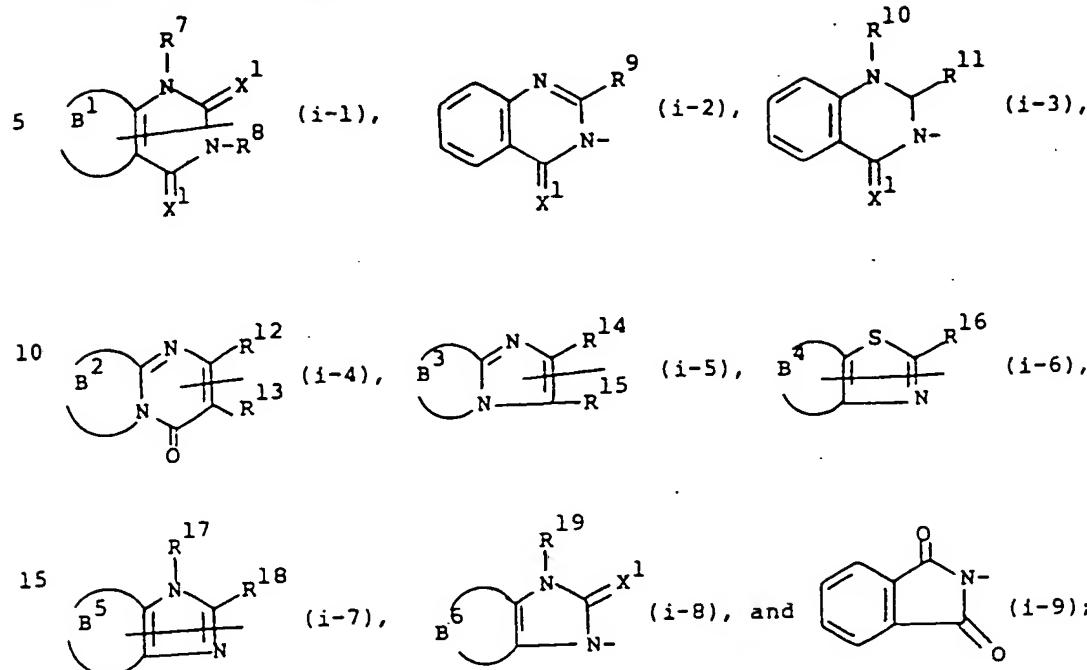
independently selected from the group consisting of halo, hydroxy, nitro, cyano, trifluoromethyl, lower alkyl, lower alkyloxy, lower alkylthio, mercapto, amino, mono- and di(lower alkyl)amino, carboxyl, lower alkyloxycarbonyl and lower alkyl-CO-; thienyl; 5 halothienyl; furanyl; lower alkyl substituted furanyl; pyridinyl; pyrazinyl; thiazolyl and imidazolyl optionally substituted by lower alkyl; and wherein Ar² is a member selected from the group consisting of phenyl being optionally substituted with up to three substituents each independently selected from the group consisting 10 of halo, hydroxy, nitro, cyano, trifluoromethyl, lower alkyl, lower alkyloxy, lower alkylthio, mercapto, amino, mono- and di(lower alkyl)amino, carboxyl, lower alkyloxycarbonyl and (lower alkyl)-CO.

As used in the foregoing definitions the term "halo" is generic to fluoro, chloro, bromo and iodo; the term "lower alkyl" is meant 15 to include straight and branch chained saturated hydrocarbon radicals having from 1 to 6 carbon atoms such as, for example, methyl, ethyl, 1-methylethyl, 1,1-dimethylethyl, propyl, 2-methylpropyl, butyl, pentyl, hexyl and the like; "alkyl" is meant to include lower alkyl radicals, as defined hereinabove, and the higher homologs thereof 20 having from 7 to 10 carbon atoms; the term "cycloalkyl" is generic to cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl; and "lower alkanediyl" is meant to include bivalent straight or branch chained alkanediyl radicals having from 1 to 6 carbon atoms.

It is evident that in the compounds of formula (I) the bicyclic 25 condensed ring system may be unsaturated or partly or completely saturated.

The compounds of formula (I) wherein Het is a heterocycle which is substituted with a hydroxy, mercapto or amino radical may contain in their structure a keto-enol tautomeric system or a vinylog system 30 thereof and consequently these compounds may be present in their keto form as well as their enol form.

Preferred compounds within the invention are those wherein Het is a member of the group consisting of



wherein each X^1 is independently O or S;

20 R^7 , R^8 , R^{10} , R^{17} and R^{19} are each independently hydrogen, lower alkyl, Ar^2 -lower alkyl, hydroxylower alkyl or lower alkyloxycarbonyl; R^9 , R^{11} , R^{12} , R^{13} , R^{14} , R^{15} , R^{16} and R^{18} are each independently hydrogen, lower alkyl, hydroxy, mercapto, lower alkyloxy, lower alkylthio, halo and (lower alkyloxycarbonyl)lower alkyl;

25 B^1 is $-CH=CH-CH=CH-$, $-S-CH=CH-$ or $-N=CH-NH-$;

B^2 is $-CH=CH-CH=CH-$, $-S-(CH_2)_2$, $-S-(CH_2)_3$, or $-(CH_2)_4$;

30 B^3 is $-CH=CH-CH=CH-$, $-CH=N-CH=CH-$, $-CH_2-NH-(CH_2)_2-$, $-S-CH=CH-$ or $-N=CH-CH=CH-$;

B^4 is $-CH_2-NH-(CH_2)_2-$, $-N=CH-CH=CH-$ or $-N=CH-N=CH-$;

B^5 is $-N=CH-CH=CH-$, $-CH=CH-N=CH-$ or $-CH=N-CH=N-$;

B^6 is $-CH=CH-CH=CH-$ or $-CH=N-CH=N-$;

wherein one or two hydrogen atoms in said radicals B^1 , B^2 , B^3 , B^4 ,

B^5 or B^6 or in the benzene part of the radicals of formula (i-2),

(i-3) or (i-9) may be replaced by lower alkyl, lower alkylthio, lower

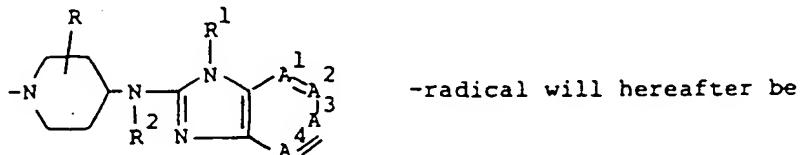
alkyloxy or halo where said hydrogen atom is bonded on a carbon atom, or by lower alkyl, lower alkyloxycarbonyl, Ar^2 -lower alkyl, where said hydrogen is bonded on a nitrogen atom.

It is clear that R^7 , R^8 , R^{12} , R^{13} , R^{14} , R^{15} , R^{16} , R^{17} or R^{18} is absent where the radical of formula (i-1), respectively (i-4), (i-5), (i-6) and (i-7) is connected to $\text{C}_{\text{s}}\text{H}_{2\text{s}}$ on the atom bearing R^7 , R^8 , R^{12} , R^{13} , R^{14} , R^{15} , R^{16} , R^{17} or R^{18} .

Particularly preferred compounds are those wherein L is a radical (g) or (h) wherein Het is as described hereinabove for the preferred compounds.

In order to simplify the structural representations of the compounds of formula (I) and of certain precursors and intermediates thereof the

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represented by the symbol D.

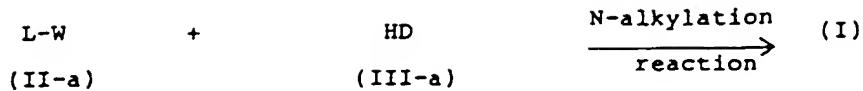
20 The compounds of formula (I) can generally be prepared by reacting an intermediate of formula (II) with a piperidine of formula (III) following art-known alkylating procedures.

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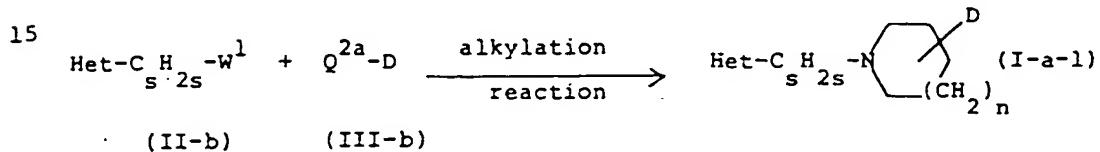
In (II) and (III) Q^1 and Q^2 are selected so that in combination with Het a bivalent radical of formula (f), (g) or (h) is formed during the alkylation reaction, said (f), (g) and (h) having the previously described meaning.

For example, the compounds of formula (I) can generally be prepared by N-alkylating a piperidine of formula (III) wherein Q^2 is hydrogen, said piperidine being represented by the formula (III-a), with a reagent of formula (II) having the general formula L-W, (II-a).



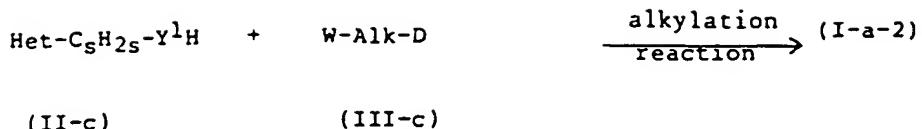
In (II-a) W represents an appropriate reactive leaving group such as, 5 for example, halo, e.g., chloro, bromo or iodo, or a sulfonyloxy group, e.g. methylsulfonyloxy or 4-methylphenylsulfonyloxy.

Additionally, the compounds of formula (I) wherein L is a radical of formula (f), a radical of formula (g) wherein Y is other than a direct bond, Y^1 , or a radical of formula (h) wherein Z is other than 10 a direct bond, Z^1 , said compounds being represented by the formulae (I-a-1), respectively (I-a-2) and (I-a-3), can be prepared by alkylating an intermediate of formula (III-b) with a reagent of formula (II-b).

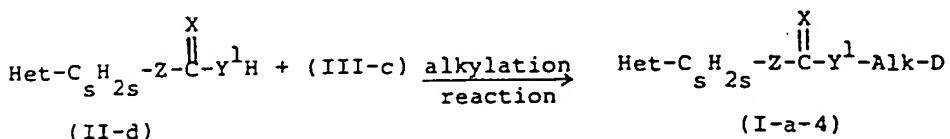


In (III-b) Q^{2a} is a radical of formula $\text{HN}\left(\text{CH}_2\right)_n^{\text{X}}$, respectively a 25 radical of formula $\text{HY}^1\text{-Alk-}$ or $\text{HZ}^1\text{--C}^{\text{X}}\text{-Y-Alk-}$. In (II-b) W^1 has the previously defined meaning of W and, where s is 0, it may also represent a lower alkyloxy, lower alkylthio or lower alkylsulfonyl group.

The compounds of formula (I-a-2) may also be prepared by alkylating a piperidine of formula (III) wherein Q^2 is a radical of formula -Alk-W, said piperidine being represented by the formula (III-c), with 30 a reagent of formula (II) wherein Q^1 is a radical of formula $-\text{C}_s\text{H}_{2s}-Y^1\text{H}$, said reagent being represented by the formula (II-c).



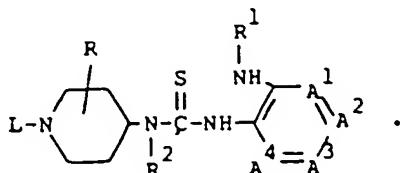
5 The compounds of formula (I) wherein L is a radical of formula
 Het-C_s^{2s}-Z-C(=X)-Y¹-Alk, said compounds being represented by
 the formula (I-a-4), may also be prepared by N-alkylating a piperidine
 of formula (III-c) with a reagent of formula (II) wherein Q² is a
 radical of formula -C_s^{2s}-Z-C(=X)-Y¹H, said reagent being represented
 10 by the formula (II-d).



15 The alkylation reactions are conveniently conducted in an inert organic solvent such as, for example, an aromatic hydrocarbon, e.g., benzene, methylbenzene, dimethylbenzene, and the like; a lower alkanol, e.g., methanol, ethanol, 1-butanol and the like; a ketone, e.g., 2-propanone, 4-methyl-2-pentanone and the like; an ether, e.g., 1,4-dioxane, 1,1'-oxybisethane, tetrahydrofuran and the like; N,N-dimethylformamide (DMF); N,N-dimethylacetamide (DMA); nitrobenzene; 1-methyl-2-pyrroli-dinone; and the like. The addition of an appropriate base such as, for example, an alkali metal carbonate or hydrogen carbonate, sodium hydride or an organic base such as, for example, N,N-diethylethanamine

20 or N-(1-methylethyl)-2-propanamine may be utilized to pick up the acid which is liberated during the course of the reaction. In some circumstances the addition of an iodide salt, preferably an alkali metal iodide, is appropriate. Somewhat elevated temperatures may enhance the rate of the reaction.

25 The compounds of formula (I) can also be prepared by the cyclo-desulfurization reaction of an appropriate thiourea derivative of the formula

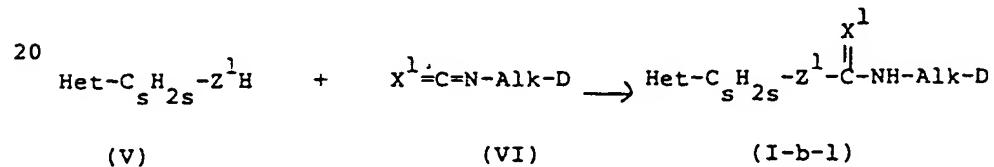


(IV)

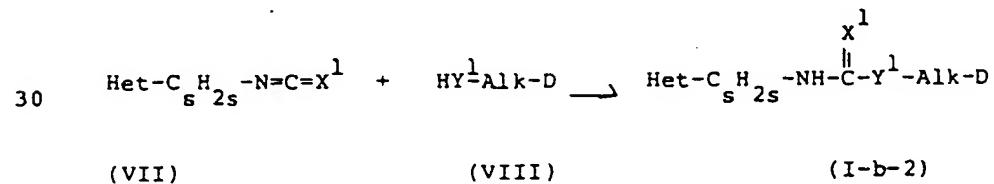
Said cyclodesulfurization reaction may be carried out by the reaction of (IV) with an appropriate alkyl halide, preferably iodomethane in an appropriate reaction-inert organic solvent, e.g., a lower alkanol such as methanol, ethanol, 2-propanol and the like.

5 Otherwise, the cyclodesulfurization reaction may be carried out by the reaction of (IV) with an appropriate metal oxide or salt in an appropriate solvent according to art-known procedures. For example, the compounds of formula (I) can easily be prepared by the reaction of (IV) with an appropriate Hg(II) or Pb(II) oxide or salt, such as, for 10 example HgO, HgCl₂, Hg(OAc)₂, PbO or Pb(OAc)₂. In certain instances it may be appropriate to supplement the reaction mixture with a small amount of sulfur. Even so methanediimines, especially N,N'-methane-tetraylbis[cyclohexanamine] may be used as cyclodesulfurizing agents.

The compounds of formula (I) wherein L is a radical of formula (h) 15 wherein Z is Z¹, Y is NH and X is O or S, said X being represented by X¹ and said compounds by the formula (I-b-1), can generally be prepared by reacting an isocyanate or isothiocyanate of formula (V) with a reagent of formula (VI).



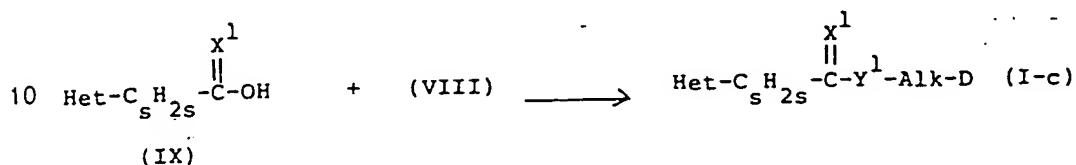
The compounds of formula (I) wherein L is a radical of formula (h) wherein Z is NH, Y is Y¹ and X is X¹, said compounds being 25 represented by the formula (I-b-2), can be prepared by reacting an isocyanate or isothiocyanate of formula (VII) with a piperidine of formula (VIII).



The reaction of (V) with (VI) and (VII) with (VIII) is generally conducted in a suitable reaction-inert solvent such as, for example, an

ether, e.g. tetrahydrofuran and the like. Elevated temperatures may be suitable to enhance the rate of the reaction.

The compounds of formula (I) wherein L is a radical of formula (h) wherein Z is a direct bond and X is X^1 , said compounds being represented by the formula (I-c), may be prepared by reacting a piperidine of formula (VIII) with a reagent of formula (IX).



The reaction of (VIII) with (IX) may generally be conducted following art-known esterification- or amidation reaction procedures. For example, the carboxylic acid may be converted into a reactive derivative, e.g. an anhydride or a carboxylic acid halide, which subsequently, is reacted with (VIII); or by reacting (VIII) and (IX) with a suitable reagent capable of forming amides or esters, e.g. 20 dicyclohexylcarbodiimide, 2-chloro-1-methylpyridinium iodide and the like. Said reactions are most conveniently conducted in a suitable solvent such as, for example, an ether, e.g. tetrahydrofuran, a halogenated hydrocarbon, e.g. dichloromethane, trichloromethane or a polar aprotic solvent, e.g. N,N-dimethylformamide. The addition of 25 a base, e.g. N,N-diethylethanamine may be appropriate.

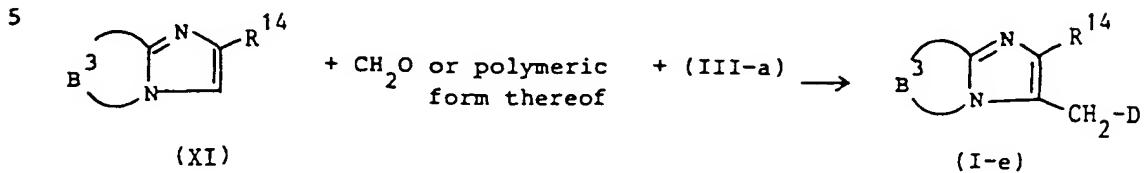
The compounds of formula (I) wherein L is a radical of formula (g) wherein Y is a direct bond and s is 0, said compounds being represented by the formula (I-d), may also be prepared by reacting an appropriate alkenylene of formula (X) with a piperidine of formula 30 (III-a) by stirring and, if desired, heating the reactants together.

Het-lower alkenediyl-H + (III-a) \longrightarrow Het-Alk-D (I-d)

(X)

The compounds of formula (I) wherein L is a radical of formula (g), wherein Het is a radical of formula (i-5) wherein R^{15} is hydrogen, 35 s is 0, Y is a direct bond and -Alk- is $-\text{CH}_2-$, said compounds being

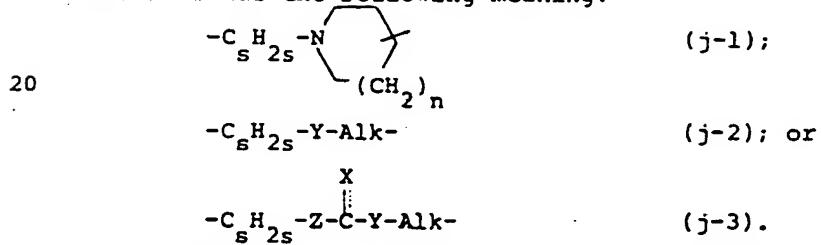
represented by the formula (I-e) may conveniently be prepared by reacting an intermediate of formula H-D (III-a) with a reagent of formula (XI) in the presence of formaldehyde or a polymeric form thereof.



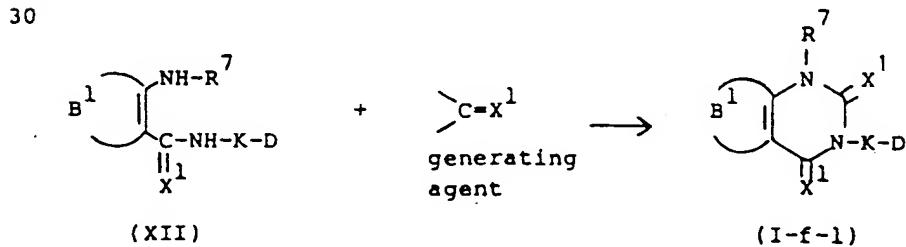
10 Said reaction may conveniently be conducted in a suitable solvent, e.g. water, acetic acid, propanoic acid or mixtures of such solvents. Elevated temperatures may be appropriate to enhance the reaction rate.

The compounds of formula (I) may also be prepared following procedures for preparing condensed bicyclic ringsystems which are known in the art or analogous procedures thereof. A number of such cyclization procedures will be described hereinafter.

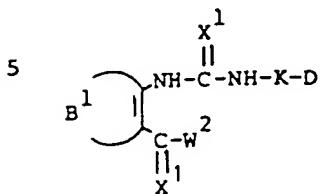
The bivalent radical K used in the description of these cyclization reactions has the following meaning:



For example, where Het is a radical of formula (i-1) being connected to K by the nitrogen atom bearing R⁸, said Het may be formed by condensing an intermediate (XII) with a >C=X¹ generating agent, e.g. urea, thiourea, 1,1'-carbonylbis[1H-imidazole], lower alkyl carbono-halide, phosgene, thiophosgene, trichloromethyl carbonohalide and the like.

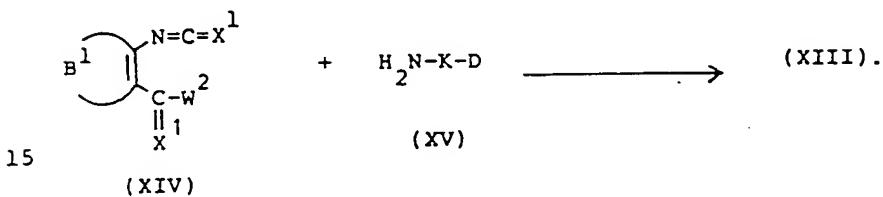


The compounds of formula (I-f-1) wherein R⁷ is hydrogen (I-f-1-a) may additionally be prepared by cyclizing an intermediate of formula



(XIII), which may in situ be generated by

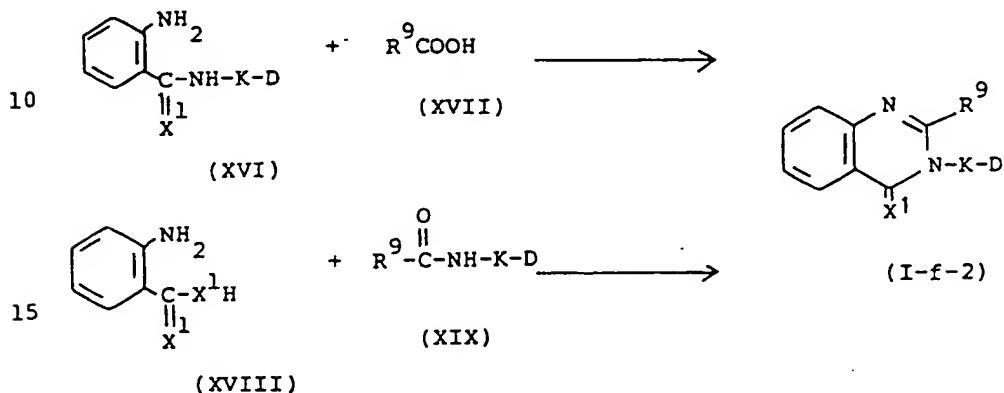
10 reacting a reagent (XIV) with an amine (XV).



W² as used throughout the description of the final compounds and intermediates is an appropriate reactive leaving group, such as, for example, halo, e.g., chloro, bromo or iodo, a sulfonyloxy group, e.g. 20 methylsulfonyloxy or 4-methylphenylsulfonyloxy, a lower alkyloxy, lower alkylthio, Ar²-oxy or Ar²-thio group.

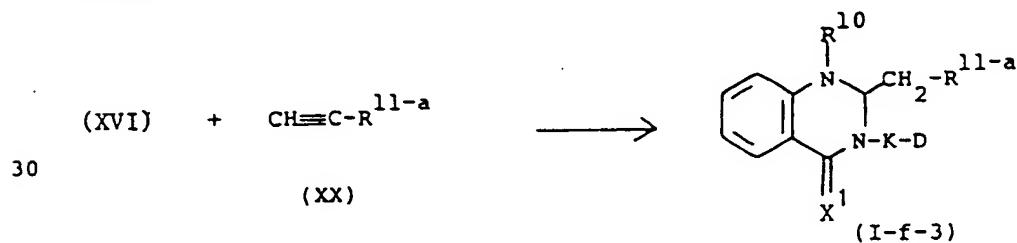
The reaction of (XII) with the $\text{C}=\text{X}^1$ generating agent and the cyclization of (XIII) may conveniently be conducted in a suitable solvent such as, for example, an ether, e.g. 1,1-oxybisethane, 25 tetrahydrofuran, an halogenated hydrocarbon, e.g. dichloromethane, trichloromethane, a hydrocarbon, e.g. benzene, methylbenzene, an alcohol, e.g. methanol, ethanol, a ketone, e.g. 2-propanone, 4-methyl-2-pentanone, N,N-dimethylformamide, N,N-dimethylacetamide, or mixtures of such solvents, optionally in the presence of an 30 appropriate base such as, for example, N,N-diethylethanamine, an alkali or earth alkaline metal carbonate or hydrogen carbonate. In order to enhance the reaction rate, it may be suitable to heat the reaction mixture.

Further, where Het is a radical of formula (i-2), said Het may be generated by cyclizing an intermediate (XVI) with an acid (XVII) or a suitable functional derivative thereof, thus giving a compound of formula (I-f-2). Alternatively an intermediate (XVIII) may be 5 condensed with an aromatic amino acid or -thioacid of formula (XIX), giving also a compound (I-f-2).



The reaction of (XVI) with (XVII) and of (XVIII) with (XIX) may be conducted in a suitable reaction-inert solvent, such as, for example, 20 a hydrocarbon, e.g. benzene, methylbenzene, an alcohol, water. In some instances it may be appropriate to use higher temperatures in order to reduce the reaction time.

Where Het is a radical of formula (i-3), said Het may be formed by reacting the previously described intermediate (XVI) with an 25 appropriate acetylene derivative (XX), thus giving a compound of formula (I-f-3).

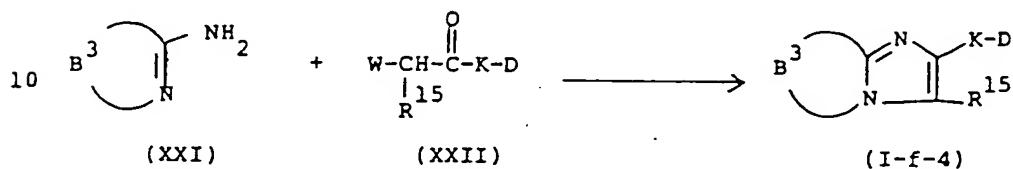


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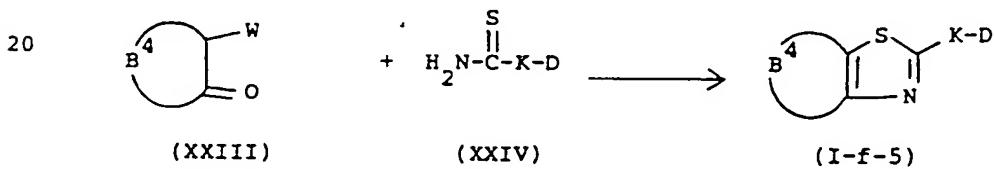
wherein $R^{11-a}-CH_2-$ is a suitable substituent on said radical (i-3).

The reaction of (XX) with (XVI) may be conducted in a suitable solvent such as, for example, an alcohol, e.g. methanol, ethanol. Elevated temperatures may also be appropriate to shorten the reaction time.

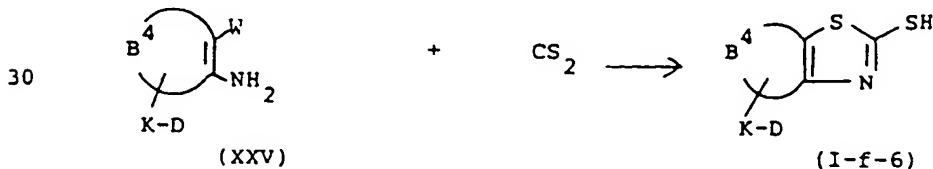
5 Additionally, where Het is a radical (i-5), said Het may be created by condensing a reagent (XXI) with an intermediate (XXII), thus giving a compound (I-f-4).



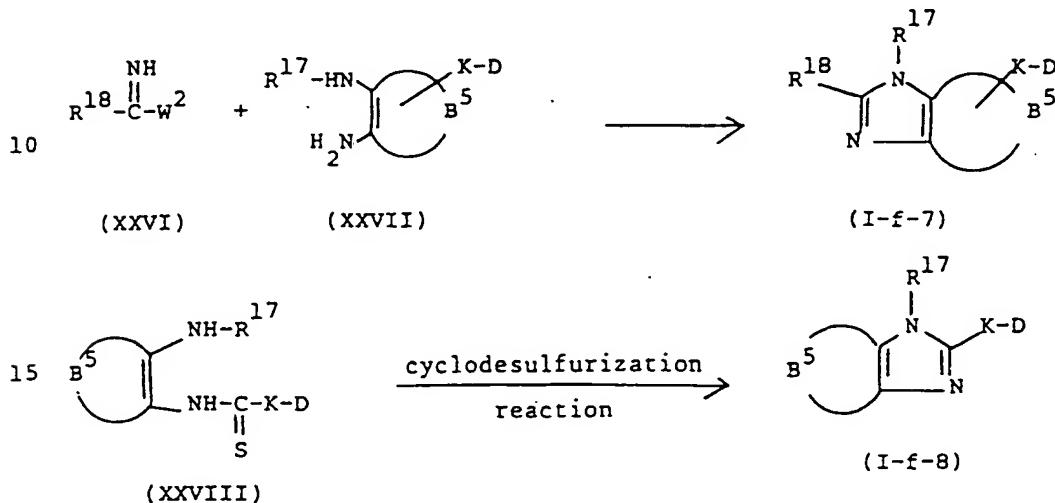
Further, where Het is a radical of formula (i-6), wherein Het is connected to K by the thiazole ring, said Het may be formed during the cyclization of a reagent (XXIII) with an intermediate (XXIV), thus giving a compound (I-f-5).



Where Het is a radical (i-6) being connected to K by the B^4 25 containing ring and bearing a 2-mercaptoposubstituent, said Het may be formed during the cyclization of an intermediate (XXV) with CS_2 , thus giving a compound (I-f-6).



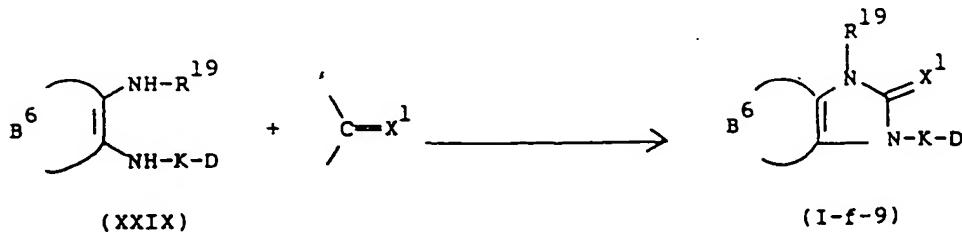
Where Het is a radical of formula (i-7) being connected to K either by the B^5 containing ring or by the imidazole ring, said Het is formed during the condensation reaction of a reagent (XXVI) with an intermediate (XXVII) respectively by the cyclodesulfurization reaction of an intermediate (XXVIII), thus giving a compound (I-f-7) respectively (I-f-8).



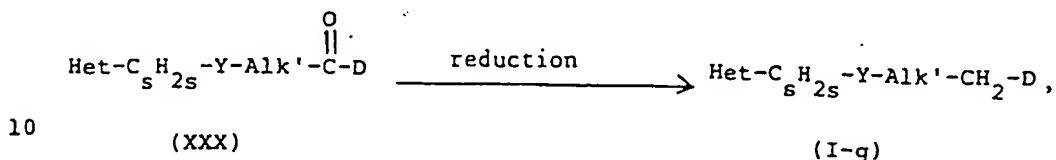
The reactions of (XXI) with (XXII), of (XXIII) with (XXIV), of (XXV) with CS_2 and (XXVI) with (XXVII) may conveniently conducted in a suitable reaction-inert solvent, such as for example one of the solvents given hereinabove for the preparation of (I-f-1) optionally in the presence of an appropriate base, e.g. one of the bases also described for the preparation of (I-f-1); higher temperatures may be used to enhance the reaction rate.

The cyclodesulfurization of (XXVIII) may be conducted following the same reaction circumstances as described hereinabove for the preparation of (I) starting from (IV).

Where Het is a radical (i-8), said Het may be formed during the condensation of an intermediate (XXIX) with a $C=X^1$ generating agent, following the same procedures as previously described for the preparation of (I-f-1) starting from (XII).



The compounds of formula (I) wherein L is a radical of formula (g), said compounds being represented by the formula (I-g), may also be generated by reducing an intermediate (XXX) with an appropriate complex metal hydride, e.g. lithium aluminium hydride, in a suitable solvent such as, for example, an ether, e.g. tetrahydrofuran, 5 1,1'-oxybisethane and the like.



Alk' having the previously defined meaning of Alk, provided that one methylene function is missing.

The compounds of formula (I) can also be converted into each 15 other following art-known procedures of functional grouptransformation. Some examples will be cited hereinafter.

The compounds of formula (I) having a nitro substituent can be converted into their corresponding amines by stirring and, if desired, heating the starting nitro-compounds in a hydrogen-20 containing medium in the presence of a suitable amount of an appropriate catalyst such as, for example, platinum-on-charcoal, palladium-on-charcoal, Raney-nickel and the like catalysts.

Suitable solvents are, for example, alcohols, e.g. methanol, ethanol and the like.

25 Halo atoms substituted on aryl groups may be replaced by hydrogen following art-known hydrogenolysis procedures, i.e. by stirring and, if desired, heating the starting compounds in a suitable solvent under hydrogen atmosphere in the presence of an appropriate catalyst, e.g. palladium-on-charcoal and the like catalysts. Said halo atoms may also 30 be replaced by a lower alkyloxy or a lower alkylthio substituent by reacting the starting halo-compound with an appropriate alcohol or thioalcohol or, preferably, an alkali- or earth alkaline metal salt or an appropriate alcohol or thioalcohol in a suitable solvent.

The compounds of formula (I) wherein L is a radical (g) wherein Y 35 is NH can be converted into a compound of formula (I) wherein L is a

radical (g) wherein Y is N-CO(lower alkyl) or N-CO(Ar^2) by reacting the starting amine with an appropriate carboxylic acid or a derivative thereof such as, for example, an acid halide, an acid anhydride and the like.

5 The compounds of formula (I) wherein L is a radical (g) wherein Y is NH can be converted into a compound of formula (I) wherein L is a radical (g) wherein Y is N-CO(lower alkylamino), N-CO-NH- Ar^2 , N-CS(lower alkylamino) or N-CS-NH- Ar^2 by reacting the starting amine with an appropriate isocyanate or isothiocyanate in a suitable solvent.

10 The compounds of formula (I) having an Het substituted with a thio (=S) radical may be converted into the corresponding oxo (=O) analogs by reacting the former compounds with a peroxide, e.g. hydrogen peroxide, in a suitable solvent.

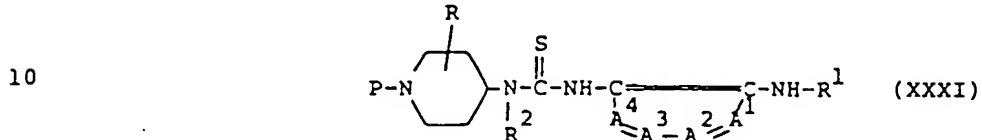
Compounds of formula (I) containing an Het which is unsaturated may 15 be converted into the corresponding compounds wherein Het is saturated or partly saturated following art-known reducing procedures.

In all of the foregoing and in the following preparations, the reaction products may be isolated from the reaction mixture and, if necessary, further purified according to methodologies generally 20 known in the art.

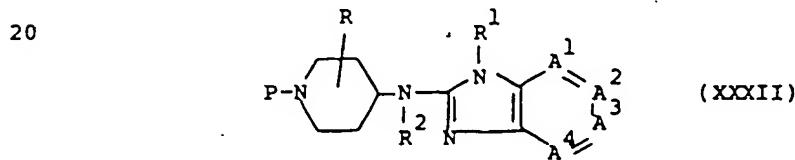
The compounds of formula (I) have basic properties and, consequently, they may be converted to their therapeutically active non-toxic acid addition salt forms by treatment with appropriate acids, such as, for example, inorganic acids, such as hydrohalic 25 acid, e.g. hydrochloric, hydrobromic and the like, and sulfuric acid, nitric acid, phosphoric acid and the like; or organic acids, such as, for example, acetic, propanoic, hydroxyacetic, 2-hydroxypropanoic, ethanedioic, 2-oxopropanoic, propanedioic, butanedioic, (Z)-2-butenedioic, (E)-2-butenedioic, 2-hydroxybutanedioic, 30 2,3-dihydroxybutanedioic, 2-hydroxy-1,2,3-propanetricarboxylic, methanesulfonic, ethanesulfonic, benzenesulfonic, 4-methylbenzenesulfonic, cyclohexanesulfamic, 2-hydroxybenzoic, 4-amino-2-hydroxybenzoic and the like acids. Conversely the salt form can be converted by treatment with alkali into the free base form.

Some intermediates and starting materials in the foregoing preparations are known compounds which may be prepared according to art-known methodologies of preparing said or similar compounds and others are new. A number of such preparation methods will be described 5 hereinafter in more detail.

The intermediates of formula (III-a) can conveniently be prepared starting from a thiourea derivative of formula



wherein P is an appropriate protective group such as, for example, lower alkyloxycarbonyl, $\text{Ar}^2\text{-CH}_2\text{-O-CO-}$, $\text{Ar}^2\text{-CH}_2\text{-}$ and the like, 15 by a cyclodesulfurization reaction following the same procedure as described hereinabove for the preparation of (I) starting from (IV) and, subsequently eliminating the protective group P in the thus obtained intermediate of formula

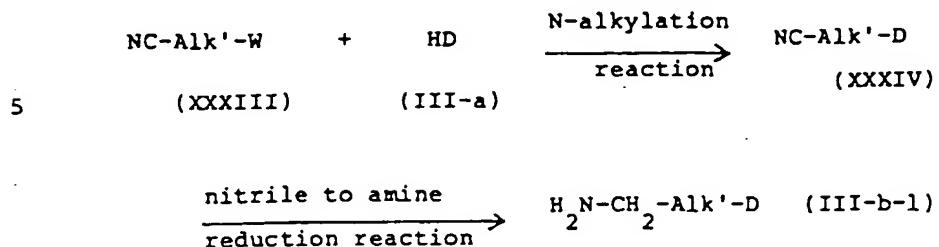


The elimination of the protective group P in (XXXII) may generally be carried out following art-known procedures such as, for example, by 25 hydrolysis in alkaline or acidic aqueous medium.

The intermediates of formula (III-b) and (III-c) may be derived from the corresponding intermediates of formula (III-a) by reacting the latter with a suitable reagent following art-known N-alkylating procedures.

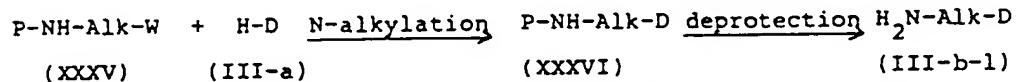
30 For example, intermediates of formula (III-b) wherein Q^{2a} represents a radical of formula $\text{H}_2\text{N-CH}_2\text{-Alk}'\text{-}$, (III-b-1), can also be prepared by reacting an intermediate of formula (III-a) with a nitrile of formula (XXXIII) following art-known N-alkylating procedures and subsequently converting the thus obtained nitrile (XXXIV) into 35 the corresponding amine (III-b-1) following art-known nitrile to amine

reducing procedures, e.g., by catalytically hydrogenating procedures and the like.

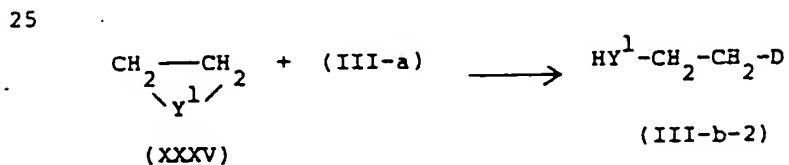


10 In (XXXIII), (XXXIV) and (III-b-1) Alk' has the same meaning as Alk provided that one methylene function is missing.

The intermediates of formula (III-b-1) may alternatively be prepared by reacting a reagent (XXXV) with (III-a) following art-known N-alkylating procedures and subsequently converting the thus formed intermediate (XXXVI) into the free amine following art-known deprotection procedures.



20 The intermediates of formula (III-b) wherein Q^{2a} represents a radical of formula $HY^1-CH_2-CH_2-$, (III-b-2), may also be prepared by the reaction of (III-a) with a reagent of formula (XXXV) by stirring and, if desired, heating the reactants together in a suitable solvent.

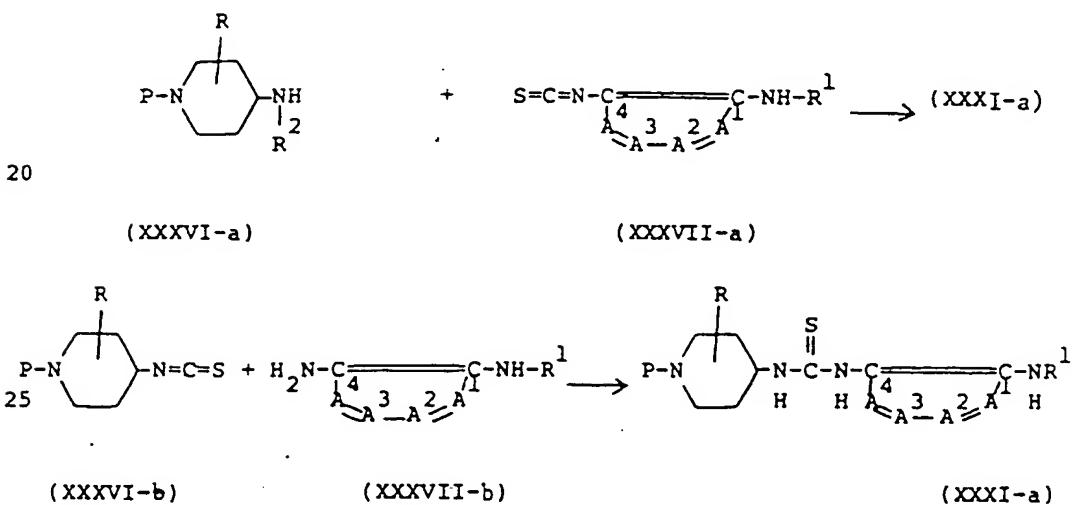


30 The intermediates of formula (III-b) wherein Q^{2a} is a radical of formula $HY^1\text{-Alk-}$, (III-d), may be converted into an intermediate of formula (III-c) by converting the function Y^1H into an appropriate leaving group, e.g., where Y^1 is O, by converting a hydroxy function into a chloro atom, with thionyl chloride, phosphoryl chloride and the
 35 like.

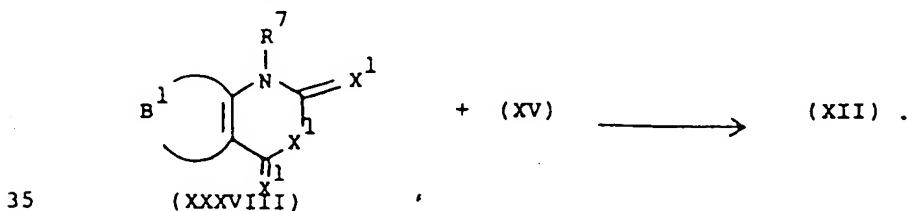
The intermediates of formula (III-b-1) may also be derived from an appropriate corresponding carbonyl-oxidated form by reacting said carbonyl-oxidated form with hydroxylamine and reducing the thus obtained oxime following art-known methods, e.g., catalytic 5 hydrogenation and the like reducing methods.

During one of the reactions the intermediates wherein R¹ and/or R² and/or R³ and/or R⁴ is hydrogen may be converted into the corresponding intermediates wherein R¹ and/or R² and/or R³ and/or R⁴ is other than hydrogen following art-known N-alkylating, N-acylating or 10 reductive N-alkylating procedures.

The intermediates of formula (XXXI) and the intermediates of formula (XXXI), wherein R² is hydrogen, said intermediates being represented by the formula (XXXI-a), may be prepared by reacting a piperidine of formula (XXXVI-a) or (XXXVI-b) with an aromatic reagent of formula 15 (XXXVII-a) or (XXXVII-b).



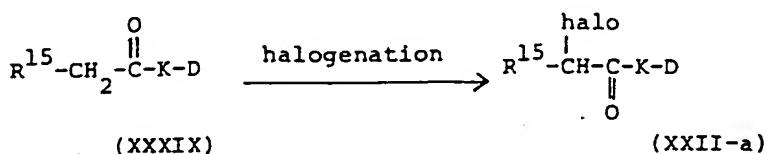
The intermediates of formula (XII) can conveniently be prepared by 30 reacting an intermediate (XV) with a reagent of formula (XXXVIII)



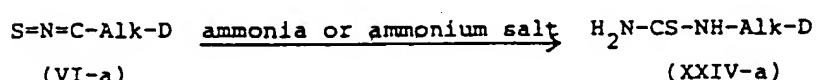
The intermediates of formula (XV) may be prepared by N-alkylating an intermediate (III-a) with a suitable N-protected reagent, followed by an appropriate deprotection reaction.

The intermediates of formula (XIX) may be prepared by N-alkylating 5 (III-a) with a reagent $R^9-CO-NH-K-W$.

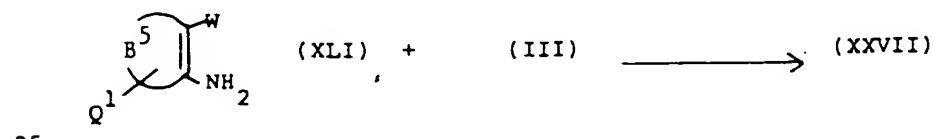
The intermediates of formula (XXII) wherein W is halo, said intermediates being represented by the formula (XXII-a), can be prepared by halogenating an intermediate (XXXIX), which can be prepared by N-alkylating (III-a) with a reagent of formula



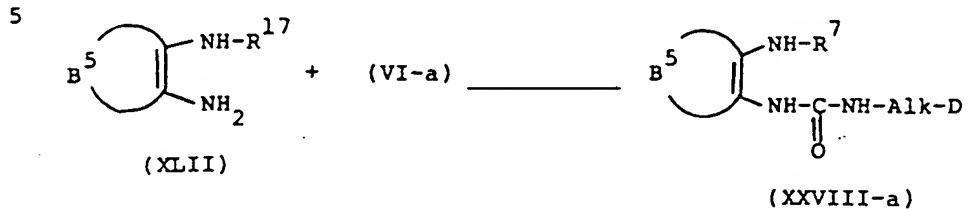
The intermediates of formula (XXIV) wherein K is -NH-Alk-, said
15 intermediates being represented by the formula (XXIV-a), may be
prepared by reacting an intermediate of formula (VI), wherein X^1 is
S, (VI-a), with ammonia or an ammonium salt, e.g. ammonium chloride,
in the presence of a suitable solvent such as, for example, a lower
alcohol, e.g. methanol.



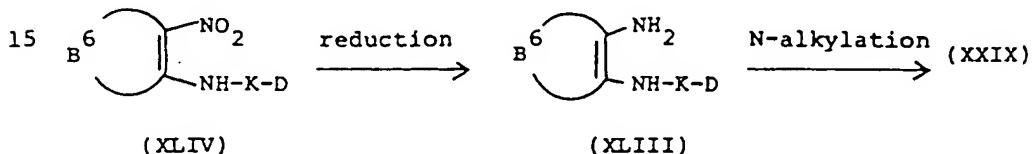
The intermediates of formula (XXV) and (XXVII) may be prepared by reacting an intermediate (III) with an appropriate reagent of formula (XL), respectively (XLI) following the same procedures as described hereinabove for the preparation of (I) starting from (II).



The intermediates of formula (XXVIII) wherein K is -NH-Alk-, said intermediates being represented by the formula (XXVIII-a), may be prepared by reacting an intermediate (VI-a) with a reagent (XLII), optionally in the presence of a suitable solvent.



10 The intermediates of formula (XXIX) can conveniently be prepared by N-alkylating an intermediate (XLIII). Said intermediate (XLIII) may be prepared by reducing an intermediate (XLIV) following art-known nitro to amine reducing procedures.



The intermediates of formula (XLIV) may be prepared by alkylating an intermediate of formula (XV) with an appropriate N-alkylating reagent.

20 The intermediates of formula (XXX) can be prepared by N-acylating an intermediate (III-a) with an appropriate reagent of formula $\text{Het-C}_{\text{s.2s}}^{\text{H}}\text{-Y-Alk'-CO-W}^2$.

The intermediates of formula (II) can conveniently be prepared following art-known procedures as described in, for example, U.S.

25 Patent Number 4,335,127, U.S. Patent Number 4,342,870 and European Patent Publication Number 0,070,053.

From formula (I) it is evident that the compounds of this invention may have several asymmetric carbon atoms in their structure. Each of these chiral centers may be present in a R- and a S-configuration, 30 this R- and S-notation being in correspondence with the rules described by R.S. Cahn, C. Ingold and V. Prelog in *Angew. Chem., Int. Ed. Engl.*, 5, 385, 511 (1966).

Pure stereochemically isomeric forms of the compounds of formula (I) may be obtained by the application of art-known procedures.

Diastereoisomers may be separated by physical separation methods such as selective crystallization and chromatographic techniques, e.g., counter current distribution, and enantiomers may be separated from each other by the selective crystallization of their diastereomeric salts with optically active acids.

Pure stereochemically isomeric forms may also be derived from the corresponding pure stereochemically isomeric forms of the appropriate starting materials, provided that the reaction occurs stereospecifically.

10 It is evident that the cis and trans diastereomeric racemates may be further resolved into their optical isomers, cis(+), cis(-), trans(+) and trans(-) by the application of methodologies known to those skilled in the art.

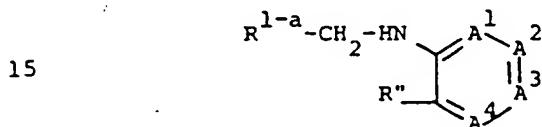
15 Stereochemically isomeric forms of the compounds of formula (I) are naturally intended to be embraced within the scope of the invention.

The following examples are intended to illustrate and not to limit the scope of the present invention. Unless otherwise stated all parts therein are by weight.

EXPERIMENTAL PARTA. Preparation of IntermediatesExample 1

A mixture of 90 parts of 4-chloro-3-nitropyridine, 71 parts of 5 4-fluorobenzenemethanamine, 63 parts of sodium carbonate and 900 parts of N,N-dimethylacetamide was stirred for 1 hour at 50°C. Water was added and the product was extracted with 4-methyl-2-pentanone. The extract was dried, filtered and evaporated. The residue was crystallized from acetonitrile. The product was filtered off and 10 dried, yielding 106 parts (75%) of N-[(4-fluorophenyl)methyl]-3-nitro-4-pyridinamine; mp. 136.8°C (intermediate 1).

In a similar manner there were also prepared:



No.	R ^{1-a}	A ¹ =A ² -A ³ =A ⁴	R''	mp. in °C
20				
2	2-furanyl	CH=CH-CH=CH	NO ₂	85.6
3	4-F-C ₆ H ₄	CH=CH-CH=N	NH ₂	-
4	4-F-C ₆ H ₄	CH=N(=O)-CH=CH	NO ₂	-
25	2-pyridinyl	N=CH-CH=CH	NO ₂	113.6
6	2-thienyl	CH=CH-CH=CH	NO ₂	-
7	4-F-C ₆ H ₄	CH=C(OCH ₃)-CH=CH	NO ₂	-
8	4-F-C ₆ H ₄	CH=CH-C(OCH ₃)=CH	NO ₂	-
9	4-F-C ₆ H ₄	CH=CH-C(CH ₃)=CH	NO ₂	99.9
30	10 2-thienyl	N=CH-CH=CH	NO ₂	-
11	3-furanyl	N=CH-CH=CH	NO ₂	-
12	5-methyl-2-furanyl	N=CH-CH=CH	NO ₂	-

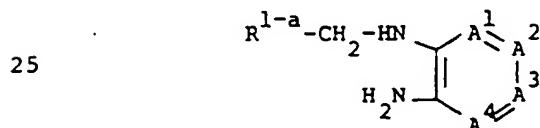
Example 2

To a stirred and cooled (0°C) solution of 8.7 parts of N-[(4-fluorophenyl)methyl]-4-nitro-3-pyridinamine, 1-oxide and 150 parts of trichloromethane was added dropwise a solution of 10.2 parts of phosphor trichloride in 75 parts of trichloromethane. Upon completion, the mixture was allowed to reach room temperature and stirring was continued for one hour at reflux temperature. The reaction mixture was cooled and the solvent was evaporated. The residue was stirred in trichloromethane. The product was filtered off and dried, yielding 9 parts of N-[(4-fluorophenyl)methyl]-4-nitro-3-pyridinamine monohydrochloride (intermediate 13).

Example 3

A mixture of 56 parts of N-(3-nitro-2-pyridinyl)-2-pyridine-methanamine, 2 parts of a solution of thiophene in ethanone 4% and 15 400 parts of methanol saturated with ammonia was hydrogenated at normal pressure and at room temperature with 4 parts of platinum-on-charcoal catalyst 5%. After the calculated amount of hydrogen was taken up, the catalyst was filtered off and the filtrate was evaporated. The residue was crystallized from acetonitrile, yielding 20 43.5 parts of N²-(2-pyridinylmethyl)-2,3-pyridinediamine; mp. 134.9°C (intermediate 14).

In a similar manner there were also prepared:



No.	R ^{1-a}	A ¹ =A ² -A ³ =A ⁴	base or mp.	
30			salt	in °C
15	2-furanyl	CH=CH-CH=CH	base	-
16	4-F-C ₆ H ₄	CH=CH-N=CH	base	163.7
17	4-F-C ₆ H ₄	CH=N-CH=CH	HCl	208.9
35	18 2-thienyl	CH=CH-CH=CH	base	-

No.	R ^{1-a}	A ¹ =A ² -A ³ =A ⁴	base or mp.	
			salt	in °C
5	19 2-furanyl	N=CH-CH=CH	base	-
	20 4-F-C ₆ H ₄	CH=C(OCH ₃)-CH=CH	base	-
	21 4-F-C ₆ H ₄	CH=CH-C(OCH ₃)=CH	base	-
	22 4-F-C ₆ H ₄	CH=CH-C(CH ₃)=CH	base	-
	23 2-thienyl	N=CH-CH=CH	base	-
10	24 3-furanyl	N=CH-CH=CH	base	-
	25 5-methyl-2-furanyl	N=CH-CH=CH	base	-

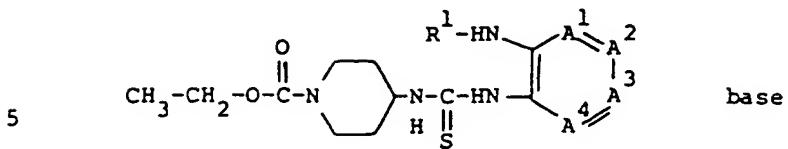
Example 4

15 To a stirred and cooled mixture of 4 parts of sodium hydroxide in 60 parts of water were added successively 7.9 parts of carbon disulfide and 17.2 parts of ethyl 4-amino-1-piperidinecarboxylate at a temperature below 10°C. Stirring was continued for 30 minutes at this temperature. Then there were added dropwise 10.9 parts of ethyl 20 carbonochloride (exothermic reaction: temp. rises to about 35°C). Upon completion, stirring was continued for 2 hours at 60°C. The reaction mixture was cooled and the product was extracted with methylbenzene. The extract was dried, filtered and evaporated, yielding 22 parts (100%) of ethyl 4-isothiocyanato-1-piperidine-25 carboxylate as a residue (intermediate 26).

Example 5

A mixture of 54 parts of ethyl 4-isothiocyanato-1-piperidinecarboxylate, 48 parts of N²-(2-furanylmethyl)-2,3-pyridinediamine and 450 parts of tetrahydrofuran was stirred and refluxed 30 overnight. The reaction mixture was evaporated and the residue was crystallized from a mixture of 2-propanone and 2,2'-oxybispropane. The product was filtered off and dried, yielding 76 parts (75%) of ethyl 4-[[2-[(2-furanylmethyl)amino]-3-pyridinyl]aminothioxo-methyl]amino]-1-piperidinecarboxylate; mp. 132.7°C (intermediate 27).

In a similar manner there were also prepared:



No.	R ¹	A ¹ =A ² -A ³ =A ⁴	mp.
			in °C
10			
28	2-furanyl methyl	CH=CH-CH=CH	-
29	4-F-C ₆ H ₄ -CH ₂	CH=CH-CH=N	-
30	4-F-C ₆ H ₄ -CH ₂	CH=CH-N=CH	166.0
31	4-F-C ₆ H ₄ -CH ₂	CH=N-CH=CH	-
15	32 2-pyridinyl methyl	N=CH-CH=CH	-
	33 H	CH=CF-CF=CH	-
	34 2-thienyl methyl	CH=CH-CH=CH	-
	35 4-F-C ₆ H ₄ -CH ₂	CH=CH-C(OCH ₃)=CH	-
	36 4-F-C ₆ H ₄ -CH ₂	CH=C(OCH ₃)=CH=CH	-
20	37 4-F-C ₆ H ₄ -CH ₂	CH=CH-C(CH ₃)=CH	-
	38 cyclohexyl	CH=CH-CH=CH	-
	39 2-thienyl methyl	N=CH-CH=CH	-
	40 3-furanyl methyl	N=CH-CH=CH	-
25	41 5-methyl-2-furanyl -methyl	N=CH-CH=CH	-

Example 6

A mixture of 42.5 parts of ethyl 4-[(phenylmethyl)-amino]-1-30 piperidinecarboxylate, 30 parts of 1-isothiocyanato-2-nitrobenzene and 270 parts of tetrahydrofuran was stirred for 3 hours at room temperature. 2,2'-Oxybispropane was added and stirring was continued overnight. The precipitated product was filtered off and dried, yielding 48.5 parts (68.5%) of ethyl 4-[[[(2-nitrophenyl)amino]-

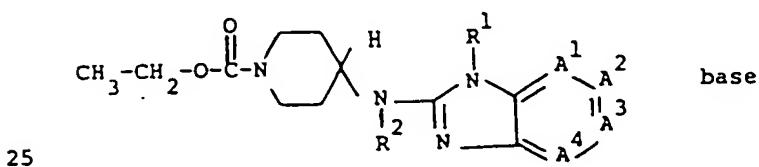
amino)thioxomethyl)(phenylmethyl)amino)-1-piperidinecarboxylate; mp. 140°C (intermediate 42).

A mixture of 48.5 parts of ethyl 4-[[[(2-nitrophenyl)-amino]-amino]thioxomethyl](phenylmethyl)amino]-1-piperidinecarboxylate and 5 600 parts of methanol, saturated with ammonia, was hydrogenated at normal pressure and at 30°C with 15 parts of palladium-on-charcoal catalyst 10%. After the calculated amount of hydrogen was taken up, the catalyst was filtered off over Hyflo and the filtrate was evaporated, yielding 47 parts (100%) of ethyl 4-[[[(2-aminophenyl)-amino]amino]thioxomethyl](phenylmethyl)amino]-1-piperidinecarboxylate 10 as a residue (intermediate 43).

Example 7

A mixture of 74 parts of ethyl 4-[[2-[(2-furanylmethyl)amino]-3-pyridinyl]aminothioxomethyl]amino]-1-piperidinecarboxylate, 96 parts of mercury(II)oxide, 0.1 parts of sulfur and 800 parts of ethanol was stirred and refluxed for 3 hours. The reaction mixture was filtered over Hyflo and the filtrate was evaporated. The residue was crystallized from acetonitrile, yielding 52.5 parts (79%) of ethyl 4-[(3-(2-furanylmethyl)-3H-imidazo[4,5-b]pyridin-2-yl)amino]-1-piperidinecarboxylate; mp. 149.2°C (intermediate 44).

In a similar manner there were also prepared:



No.	R ¹	R ²	A ¹ -A ² -A ³ -A ⁴	mp. in °C
30				
45	2-furanylmethyl	H	CH=CH-CH=CH	135.8
46	4-F-C ₆ H ₄ -CH ₂	H	CH=CH-CH=N	212.5
47*	4-F-C ₆ H ₄ -CH ₂	H	CH=CH-N=CH	-
48*	4-F-C ₆ H ₄ -CH ₂	H	CH-N-CH=CH	168.6

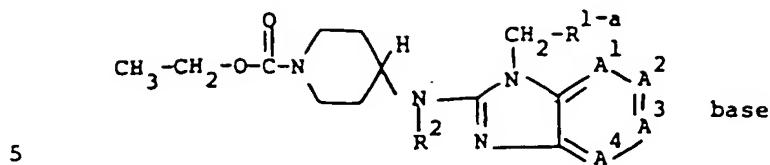
No.	R ¹	R ²	A ¹ =A ² -A ³ =A ⁴	mp.
				in °C
5	49 2-thienylmethyl	H	CH=CH-CH=CH	142.7
	50 2-pyridinylmethyl	H	N=CH-CH=CH	141.3
	51 H	H	CH=CF-CF=CH	234.9
	52 4-F-C ₆ H ₄ CH ₂	H	CH=CH-C(OCH ₃)=CH	-
	53 4-F-C ₆ H ₄ CH ₂	H	CH=C(OCH ₃)=CH=CH	-
10	54 H	C ₆ H ₅ CH ₂	CH=CH-CH=CH	-
	55 4-F-C ₆ H ₄ CH ₂	H	CH=CH-C(CH ₃)=CH	202.0
	56 cyclohexyl	H	CH=CH-CH=CH	-
	57 2-thienylmethyl	H	N=CH-CH=CH	-
	58 3-furanyl methyl	H	N=CH-CH=CH	-
15	59 5-methyl-2-furanyl-H	methyl	N=CH-CH=CH	-

* : dihydrochloride monohydrate.

20 Example 8

A mixture of 57.5 parts of ethyl 4-(1H-benzimidazol-2-ylamino)-1-piperidinecarboxylate, 33 parts of 2-(chloromethyl)pyridine hydrochloride, 43 parts of sodium carbonate, 0.1 parts of potassium iodide and 630 parts of N,N-dimethylformamide was stirred and heated 25 overnight at 70°C. The reaction mixture was cooled and poured onto water. The product was extracted with 4-methyl-2-pentanone. The extract was dried, filtered and evaporated. The residue was purified by column chromatography over silica gel using a mixture of trichloromethane and methanol (96:4 by volume) as eluent. The pure 30 fractions were collected and the eluent was evaporated. The residue was crystallized from 4-methyl-2-pentanone, yielding 30 parts (40%) of ethyl 4-[(1-[(2-pyridinyl)methyl]-1H-benzimidazol-2-yl)amino]-1-piperidinecarboxylate; mp. 161.5°C (intermediate 60).

In a similar manner there were also prepared:

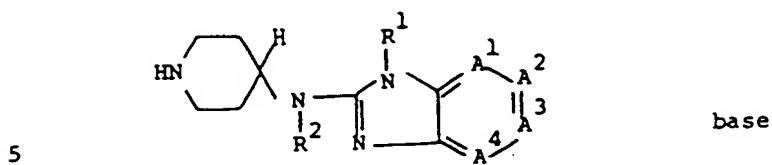


No.	R ^{1-a}	R ²	A ¹ =A ² -A ³ =A ⁴	mp. in °C
10				
61	3-pyridinyl	H	CH=CH-CH=CH	191.4
62	2-pyrazinyl	H	CH=CH-CH=CH	178.5
				179.3
63	4-F-C ₆ H ₄	H	CH=CF-CF=CH	182.3
15				
64	4-thiazolyl	H	CH=CH-CH=CH	156.2
65	4-F-C ₆ H ₄	CH ₃	CH=CH-CH=CH	-
66	3-CH ₃ -C ₆ H ₄	H	CH=CH-CH=CH	-
67	4-F-C ₆ H ₄	C ₆ H ₅ -CH ₂	CH=CH-CH=CH	-
20				

Example 9

A mixture of 50 parts of ethyl 4-[(3-(2-furanylmethyl)-3H-imidazo[4,5-b]pyridin-2-yl]amino]-1-piperidinecarboxylate, 50 parts of potassium hydroxide, 400 parts of 2-propanol and 20 drops of water was stirred and refluxed for about 5 hours. The reaction mixture was evaporated and water was added to the residue. The product was extracted twice with 4-methyl-2-pentanone. The combined extracts were dried, filtered and evaporated. The solid residue was stirred in 1,1'-oxybisethane. The product was filtered off and dried, yielding 34 parts (85%) of 3-(2-furanylmethyl)-N-(4-piperidinyl)-3H-imidazo[4,5-b]pyridin-2-amine; mp. 159.0 °C (intermediate 68).

In a similar manner there were also prepared:

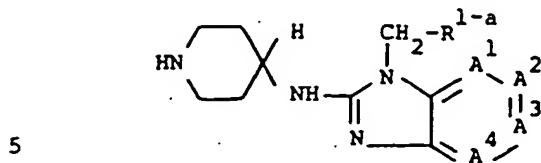


No.	R ¹	R ²	A ¹ =A ² -A ³ =A ⁴	mp. in °C
10				
69	2-furanylmethyl	H	CH=CH-CH=CH	211.0
70	2-thienylmethyl	H	CH=CH-CH=CH	-
71	4-F-C ₆ H ₄ CH ₂	H	CH=CH-C(OCH ₃)=CH	-
72*	4-F-C ₆ H ₄ CH ₂	CH ₃	CH=CH-CH=CH	222.2
73	4-F-C ₆ H ₄ CH ₂	H	CH=C(OCH ₃)-CH=CH	-
74	4-F-C ₆ H ₄ CH ₂	H	CH=CH-C(CH ₃)=CH	-
75	4-F-C ₆ H ₄ CH ₂	C ₆ H ₅ - CH ₂	CH=CH-CH=CH	-
15				
76	cyclohexyl	H	CH=CH-CH=CH	180.0
77	2-thienylmethyl	H	N=CH-CH=CH	-
78	3-furanylmethyl	H	N=CH-CH=CH	-
79	5-methyl-2-furanyl- methyl		N=CH-CH=CH	-
20				
25	* : dihydrochloride monohydrate.			

Example 10

A mixture of 30 parts of ethyl 4-[(1-[(2-pyridinyl)methyl]-1H-benzimidazol-2-yl]amino)-1-piperidinecarboxylate and 300 parts of a hydrobromic acid solution 48% in water was stirred and heated for 3 hours at 80°C. The reaction mixture was evaporated and the residue was crystallized from methanol, yielding 41 parts (93.2%) of N-(4-piperidinyl)-1-[(2-pyridinyl)methyl]-1H-benzimidazol-2-amine trihydrobromide; mp. 295.9°C (intermediate 80).

In a similar manner there were also prepared:



No.	R ^{1-a}	A ¹ =A ² -A ³ =A ⁴	base or	mp.
			salt form	in °C
10				
81	3-pyridinyl.	CH=CH-CH=CH	3HBr	> 260
82	2-pyrazinyl	CH=CH-CH=CH	3HBr	-
83	4-F-C ₆ H ₄	CH=CH-CH=N	2HBr	+ 300.6
84	4-F-C ₆ H ₄	CH=CH-N=CH	2HBr	279.4
15				
85	2-pyridinyl	N=CH-CH=CH	3HBr	265.5
86	4-F-C ₆ H ₄	CH=N-CH=CH	2HBr.H ₂ O	291.6
87	4-F-C ₆ H ₄	CH=CF-CF=CH	2HBr	210.6
88	4-thiazolyl	CH=CH-CH=CH	2HBr.H ₂ O	223.5
89	3-CH ₃ -C ₆ H ₄	CH=CH-CH=CH	2HBr	-
20				

Example 11

50 Parts of 1-[(4-fluorophenyl)methyl]-N-(4-piperidinyl)-1H-benzimidazol-2-amine dihydrobromide were taken up in water. The free base was liberated with a sodium hydroxide solution 50% and extracted with dichloromethane. The extract was dried, filtered and evaporated. The residue was boiled in 2-propanone. The product was filtered off and dried, yielding 17 parts (87.5%) of 1-[(4-fluorophenyl)methyl]-N-(4-piperidinyl)-1H-benzimidazol-2-amine; mp. 215.5°C (intermediate 90).

Example 12

A mixture of 2.1 parts of 3-buten-2-one, 9.7 parts of 1-[(4-fluorophenyl)methyl]-N-(4-piperidinyl)-1H-benzimidazol-2-amine and 120 parts of ethanol was stirred for 3 hours at reflux temperature. The reaction mixture was evaporated. The residue was purified by 35

column-chromatography over silica gel using a mixture of trichloromethane and methanol (95:5 by volume) as eluent. The pure fractions were collected and the eluent was evaporated. The residue was crystallized from a mixture of 2-propanone and 2,2'-oxybispropane, 5 yielding 5 parts (42%) of 4-[4-[(1-[(4-fluorophenyl)methyl]-1H-benzimidazol-2-yl)amino]-1-piperidinyl]-2-butanone; mp. 131.3°C (intermediate 91).

A stirred solution of 47.5 parts of 4-[4-[(1-[(4-fluorophenyl)methyl]-1H-benzimidazol-2-yl)amino]-1-piperidinyl]-2-butanone and 10 500 parts of acetic acid was acidified with a hydrobromic acid solution in glacial acetic acid. Then there were added dropwise 11.8 parts of bromine dissolved in acetic acid. Upon completion, stirring was continued overnight at room temperature. The precipitated product was filtered off and suspended in 2-propanone. The product 15 was filtered off and dried, yielding 23 parts (48.3%) of 1-bromo-4-[4-[(1-[(4-fluorophenyl)methyl]-1H-benzimidazol-2-yl)amino]-1-piperidinyl]-2-butanone dihydrobromide (intermediate 92).

Example 13

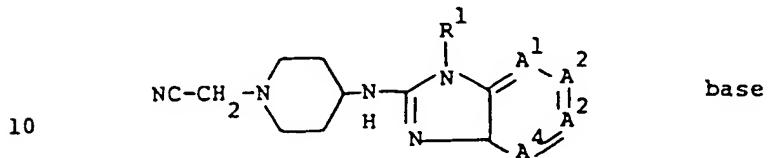
A mixture of 9 parts of oxirane, 3.24 parts of 1-(4-fluorophenyl)-20 methyl-N-(4-piperidinyl)-1H-benzimidazol-2-amine and 400 parts of methanol was stirred first overnight at room temperature and further for 4 hours at 50°C. The reaction mixture was evaporated. The residue was purified by column-chromatography over silica gel using a mixture of trichloromethane and methanol, saturated with ammonia, 25 (95:5 by volume) as eluent. The pure fractions were collected and the eluent was evaporated. The residue was crystallized from a mixture of 4-methyl-2-pentanone and 2,2'-oxybispropane, yielding 15 parts of 4-[(1-(4-fluorophenyl)methyl)-1H-benzimidazol-2-ylamino]-1-piperidineethanol; mp. 138.7°C (intermediate 93).

30 Example 14

A mixture of 11.5 parts of 4-chlorobutanenitrile, 48.5 parts of 1-(4-fluorophenylmethyl)-N-(4-piperidinyl)-1H-benzimidazol-2-amine dihydrobromide, 30 parts of sodium carbonate and 270 parts of N,N-dimethylformamide, was stirred and heated overnight at 70°C. The 35 reaction mixture was poured onto water and the product was extracted

with trichloromethane. The extract was dried, filtered and evaporated. The residue was crystallized twice from a mixture of 4-methyl-2-pentanone and 2,2'-oxybispropane, yielding 2.2 parts (80%) of 4-[(1-[(4-fluorophenyl)methyl]-1H-benzimidazol-2-yl)-5-amino]-1-piperidinebutanenitrile; mp. 130.5°C (intermediate 94).

In a similar manner there were also prepared:



No.	R ¹	..A ¹ =A ² -A ³ =A ⁴ ..	mp. °C
95	4-F-C ₆ H ₄ -CH ₂	-N=CH-CH=CH-	183.7
15 96	(2-pyridinyl)methyl	-CH=CH-CH=CH-	152.6
97*	4-F-C ₆ H ₄ -CH ₂	-CH=CH-CH=N-	173.9
98	(2-furanyl)methyl	-CH=CH-CH=CH-	194.4
99	(2-pyridinyl)methyl	-N=CH-CH=CH-	170.0
100	(2-furanyl)methyl	-N=CH-CH=CH-	157.0
20 101	(2-thienyl)methyl	-CH=CH-CH=CH-	191.7
102	C ₆ H ₅ -CH ₂	-CH=CH-CH=CH-	180.4
103	4-F-C ₆ H ₄ -CH ₂	-CH=CH-C(OCH ₃)=CH	174.8
104	4-F-C ₆ H ₄ -CH ₂	-CH=C(OCH ₃)-CH=CH	222.0
105	phenyl	-CH=CH-CH=CH-	-
25 106	3-CH ₃ C ₆ H ₄ -CH ₂	-CH=CH-CH=CH-	-

* : hemihydrate

In a similar manner there was also prepared:

4-[(1-(2-furanyl)methyl)-1H-benzimidazol-2-yl]amino]-1-piperidine-30 butanenitrile (intermediate 107).

Example 15

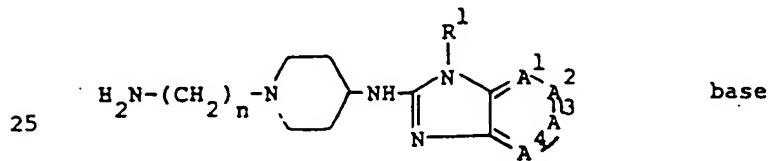
To a stirred mixture of 2.5 parts of lithium aluminum hydride and 225 parts of tetrahydrofuran was added dropwise a solution of 13 parts of 4-[(1-(2-thienyl)methyl)-1H-benzimidazol-2-yl]amino]-1-35 piperidineacetonitrile in tetrahydrofuran under nitrogen atmosphere.

Upon completion, stirring was continued for 3 hours at reflux. The reaction mixture was cooled in an ice bath and decomposed by the successive additions of 2.5 parts of water, 7.5 parts of a sodium hydroxide solution 15% and 7.5 parts of water. The whole was 5 filtered over Hyflo and the filtrate was evaporated. The residue was crystallized from acetonitrile, yielding 9.5 parts (72%) of N-[1-(2-aminoethyl)-4-piperidinyl]-1-(2-thienylmethyl)-1H-benz-imidazol-2-amine; mp. 137.1°C (intermediate 108).

Example 16

10 A mixture of 12 parts of 4-[[1-[(4-fluorophenyl)methyl]-1H-imidazo[4,5-b]pyridin-2-yl]amino]-1-piperidineacetonitrile and 200 parts of methanol saturated with ammonia was hydrogenated at normal pressure and at room temperature with 2 parts of Raney-nickel catalyst. After the calculated amount of hydrogen was taken up, the 15 catalyst was filtered off and the filtrate was evaporated. The residue was crystallized from acetonitrile, yielding 10 parts (78%) of N-[1-(2-aminoethyl)-4-piperidinyl]-1-[(4-fluorophenyl)methyl]-1H-imidazo[4,5-b]pyridin-2-amine monohydrate; mp. 116.9°C (intermediate 109).

20 Following the same procedure and using equivalent amounts of the appropriate starting materials, there were also prepared:



No.	n	R ¹	-A ¹ =A ² -A ³ =A ⁴ -	mp. in °C
110	4	4-F-C ₆ H ₄ -CH ₂	-CH=CH-CH=CH-	-
30	111	2	4-F-C ₆ H ₄ -CH ₂	-N=CH-CH=CH- 174.5
112	2	(2-pyridinyl)methyl	-CH=CH-CH=CH-	145.1
113	2	(2-furanyl)methyl	-CH=CH-CH=CH-	163.0
114	2	(2-pyridinyl)methyl	-N=CH-CH=CH-	151.1
115*	2	(2-furanyl)methyl	-N=CH-CH=CH-	182.0
35	116	2	C ₆ H ₅ CH ₂	-CH=CH-CH=CH- 131.6
117	2	4-F-C ₆ H ₄ -CH ₂	-CH=CH-C(OCH ₃)=CH-	-

No.	n	R ¹	-A ¹ =A ² -A ³ =A ⁴ -	mp. in °C
5	118	2 4-F-C ₆ H ₄ -CH ₂	-CH=C(OCH ₃) ₂ -CH=CH-	-
	119	2 C ₆ H ₅	-CH=CH-CH=CH-	-
	120	2 3-CH ₃ C ₆ H ₄ -CH ₂	-CH=CH-CH=CH-	-
	121	4 (2-furanyl)methyl	-CH=CH-CH=CH-	-

* : (E)-2-butenedioate (1:3) monohydrate salt.

10 Example 17

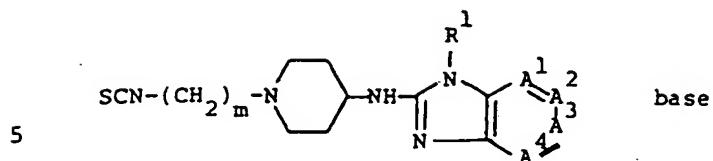
A mixture of 12 parts of N-[1-(2-aminoethyl)-4-piperidinyl]-1-[(4-fluorophenyl)methyl]-5-methoxy-1H-benzimidazol-2-amine and 150 parts of a hydrobromic acid solution 48% in water was stirred and heated for 48 hours at 80°C. The reaction mixture was evaporated and 15 the residue was suspended in 2-propanol. The product was filtered off and dried, yielding 18.5 parts (95.7%) of 2-[(1-(2-aminoethyl)-4-piperidinyl)amino]-1-[(4-fluorophenyl)methyl]-1H-benzimidazol-5-ol trihydrobromide monohydrate mp. +250°C (intermediate 122).

Example 18

20 To a stirred and cooled (-10°C) mixture of 12.6 parts of carbon disulfide, 5.2 parts of N,N'-methanetetraylbis[cyclohexanamine] and 45 parts of tetrahydrofuran was added dropwise a solution of 8.5 parts of N-[1-(2-aminoethyl)-4-piperidinyl]-1-(2-furanyl methyl)-1H-benzimidazol-2-amine in 45 parts of tetrahydrofuran. Upon completion, 25 stirring was continued overnight at room temperature. The reaction mixture was evaporated and the residue was purified by column chromatography over silica gel using trichloromethane as eluent. The pure fractions were collected and the eluent was evaporated. The residue was crystallized from acetonitrile, yielding 6.7 parts of 30 1-(2-furanyl methyl)-N-[1-(2-isothiocyanatoethyl)-4-piperidinyl]-1H-benzimidazol-2-amine (intermediate 123).

-37-

In a similar manner there were also prepared:

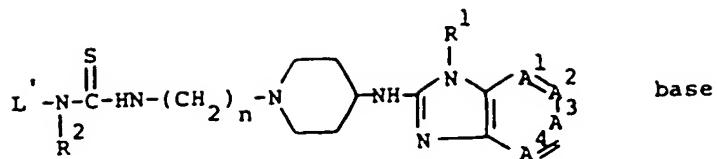


No.	m	R ¹	-A ¹ =A ² -A ³ =A ⁴ -
124	2	4-F-C ₆ H ₄ CH ₂	-CH=CH-CH=N-
125	2	(2-pyridinyl)methyl	-N=CH-CH=CH-
10	2	4-F-C ₆ H ₄ CH ₂	-N=CH-CH=CH-
126	2	(2-pyridinyl)methyl	-CH=CH-CH=CH-
127	2	C ₆ H ₅	-CH=CH-CH=CH-
128	2	(2-thienyl)methyl	-CH=CH-CH=CH-
129	2	4-F-C ₆ H ₄ CH ₂	-CH=CH-CH=CH-
130	2	4-F-C ₆ H ₄ CH ₂	-CH=CH-CH=CH-
15	3	4-F-C ₆ H ₄ CH ₂	-CH=CH-CH=CH-
131	2	(2-furanyl)methyl	-N=CH-CH=CH-
132	2		

Example 19

20 A mixture of 5.4 parts of 3,4-pyridinediamine, 16 parts of 1-(2-furanyl methyl)-N-[1-(2-isothiocyanatoethyl)-4-piperidinyl]-1H-benzimidazol-2-amine and 135 parts of tetrahydrofuran was stirred and refluxed overnight. The reaction mixture was evaporated in vacuo. The residue was purified by column chromatography over silica gel using a mixture of trichloromethane and methanol, saturated with ammonia, (95:5 by volume) as eluent. The pure fractions were collected and the eluent was evaporated, yielding 18 parts (87%) of N-(4-amino-3-pyridinyl)-N'-(2-[(4-[(1-(2-furanyl methyl)-1H-benzimidazol-2-yl)amino]-1-piperidinyl)ethyl]thiourea (intermediate 133).

25 30 Following the same procedure and using equivalent amounts of the appropriate starting materials, there were also prepared:



5

No.	L'	n R ²	R ¹	-A ¹ =A ² -A ³ =A ⁴ -	mp. °C
134	4-amino-3-pyridinyl	2 H	4-F-C ₆ H ₄ CH ₂	-CH=CH-CH=CH-	-
135	3-amino-2-pyridinyl	2 H	4-F-C ₆ H ₄ CH ₂	-CH=CH-CH=CH-	-
136	4-amino-3-pyridinyl	2 H	4-F-C ₆ H ₄ CH ₂	-CH=CH-CH=N-	-
137	4-amino-3-pyridinyl	2 H	2-pyridinylmethyl	-N=CH-CH=CH-	-
138	4-amino-3-pyridinyl	2 H	4-F-C ₆ H ₄ CH ₂	-N=CH-CH=CH-	-
139	4-amino-3-pyridinyl	2 H	2-pyridinylmethyl	-CH=CH-CH=CH-	-
140	4-amino-3-pyridinyl	2 H	C ₆ H ₅	-CH=CH-CH=CH-	-
141	4-amino-3-pyridinyl	2 H	2-thienylmethyl	-CH=CH-CH=CH-	-
142	5-amino-4-pyrimidinyl	2 H	4-F-C ₆ H ₄ CH ₂	-CH=CH-CH=CH-	-
143	4-amino-3-pyridinyl	4 H	4-F-C ₆ H ₄ CH ₂	-CH=CH-CH=CH-	-
144	4-amino-3-pyridinyl	3 H	4-F-C ₆ H ₄ CH ₂	-CH=CH-CH=CH-	-
145	4-amino-3-pyridinyl	2 H	2-furanyl methyl	-N=CH-CH=CH-	-
146	4-(methylamino)-3-pyridinyl	2 H	4-F-C ₆ H ₄ CH ₂	-CH=CH-CH=CH-	-
147	(4-F-C ₆ H ₄ CH ₂) ₂ amino-3-pyridinyl	2 H	4-F-C ₆ H ₄ CH ₂	-CH=CH-CH=CH-	-
148*	4-amino-3-pyridinyl	2 CH ₃	4-F-C ₆ H ₄ CH ₂	-CH=CH-CH=CH-	128.1

* : monohydrate

Example 20

A mixture of 120 parts of methanol saturated with ammonia and 4.1 parts of 1-(4-fluorophenylmethyl)-N-[1-(2-isothiocyanatoethyl)-4-piperidinyl]-1H-benzimidazol-2-amine was stirred overnight at room temperature. The reaction mixture was evaporated and the residue was

purified by column chromatography over silica gel using a mixture of trichloromethane and methanol (95:5 by volume), saturated with ammonia, as eluent. The pure fractions were collected and the eluent was evaporated. The residue was suspended in 1,1'-oxybisethane. The 5 product was filtered off and crystallized from acetonitrile, yielding 1.1 parts (26%) of N-[2-[4-[(1-[(4-fluorophenyl)methyl]-1H-benzimidazol-2-yl)amino]-1-piperidinyl]ethyl]thiourea; mp. 186.1°C (intermediate 149).

Example 21

10 A mixture of 3.4 parts of 6-chloro-3-nitro-2-pyridinamine, 7.4 parts of N-[1-(2-aminoethyl)-4-piperidinyl]-1-[(4-fluorophenyl)methyl]-1H-benzimidazol-2-amine and 10 parts of 1-methyl-2-pyrrolidinone was stirred and heated for 2 hours at 150°C. The reaction mixture was cooled and taken up in methanol saturated with 15 ammonia. The whole was evaporated and water was added to the residue. The product was extracted three times with 4-methyl-2-pentanone. The combined extracts were dried, filtered and evaporated in vacuo. The residue was purified by column chromatography over silica gel using a mixture of trichloromethane and methanol (95:5 by 20 volume) as eluent. The pure fractions were collected and the eluent was evaporated. The residue was crystallized from 4-methyl-2-pentanone, yielding 5 parts (50%) of N⁶-[2-[4-[(1-[(4-fluorophenyl)methyl]-1H-benzimidazol-2-yl)-amino]-1-piperidinyl]ethyl]-3-nitro-2,6-pyridinediamine; mp. 205.7°C (intermediate 150).

25 Following the same procedure and using equivalent amounts of the appropriate starting materials, there were also prepared:

1-[(4-fluorophenyl)methyl]-N-[1-[2-[(2-nitrophenyl)amino]ethyl]-4-piperidinyl]-1H-benzimidazol-2-amine; mp. 190.2°C (intermediate 151); and

30 6-chloro-N⁴-[2-[4-[(1-[(4-fluorophenyl)methyl]-1H-benzimidazol-2-yl)amino]-1-piperidinyl]ethyl]-4,5-pyrimidinediamine; mp. 216.7°C (intermediate 152).

Example 22

To a stirred mixture of 9.16 parts of 2-amino-5-(methylthio)-benzoic acid and 100 parts of 1,4-dioxane were added dropwise slowly 9.8 parts of trichloromethyl carbonochloride. Upon completion, 5 stirring was continued for 2 hours. The reaction mixture was evaporated. The residue was crystallized from acetonitrile. The product was filtered off and dried, yielding 8 parts (76%) of 6-(methylthio)-2H-3,1-benzoxazine-2,4(1H)-dione; mp. 219.4°C (intermediate 153).

10 Example 23

A mixture of 10 parts of N^6 -[2-[4-[[1-[(4-fluorophenyl)-methyl]-1H-benzimidazol-2-yl]amino]-1-piperidinyl]ethyl]-3-nitro-2,6-pyridinediamine, 3 parts of a solution of thiophene in methanol 4% and 400 parts of methanol, saturated with ammonia, was 15 hydrogenated at normal pressure and at room temperature with 4 parts of palladium-on-charcoal catalyst 10%. After the calculated amount of hydrogen was taken up, the catalyst was filtered off and the filtrate was evaporated, yielding 9 parts (94%) of N^6 -[2-[4-[[1-[(4-fluorophenyl)methyl]-1H-benzimidazol-2-yl]amino]-1-piperidinyl]-20 ethyl]-2,3,6-pyridinetriamine as a residue (intermediate 154).

In a similar manner there was also prepared:

N -[2-[4-[[1-[(4-fluorophenyl)methyl]-1H-benzimidazol-2-yl]amino]-1-piperidinyl]ethyl]-1,2-benzenediamine (intermediate 155).

Example 24

25 A mixture of 4.4 parts of N -(5-bromo-1,3,4-thiadiazol-2-yl)-acetamide, 7.3 parts of N -[1-(2-aminoethyl)-4-piperidinyl]-1-[(4-fluorophenyl)methyl]-1H-benzimidazol-2-amine, 3.18 parts of sodium carbonate and 135 parts of N,N -dimethylformamide was stirred overnight at 80-90°C. The reaction mixture was evaporated. The 30 residue was purified by column chromatography over silica gel using a mixture of trichloromethane and methanol (90:10 by volume) as eluent. The pure fractions were collected and the eluent was evaporated. The residue was crystallized from a mixture of acetonitrile and 2,2'-oxybispropane, yielding 1.7 parts of 35 N -[2-[4-[[1-[(4-fluorophenyl)methyl]-1H-benzimidazol-2-yl]amino]-1-

-41-

piperidinyl]ethyl]formamide; mp. 153.2°C (intermediate 156).

Example 25

To a stirred and hot (50°C) mixture of 4.1 parts of 2H-3,1-benzoxazine-2,4(1H)-dione and 31.5 parts of N,N-dimethylformamide 5 was added dropwise a solution of 9.4 parts of N-(1-(2-aminoethyl)-4-piperidinyl)-1-[(4-fluorophenyl)methyl]-1H-benzimidazol-2-amine in 31.5 parts of N,N-dimethylformamide at 50°C. Upon completion, stirring was continued for 3 hours at 50°C. Water was added and the product was extracted with 4-methyl-2-pentanone. The extract was 10 dried, filtered and evaporated. The residue was crystallized from acetonitrile, yielding 9.8 parts (80%) of 2-amino-N-[2-[4-[(1-(4-fluorophenyl)-methyl)-1H-benzimidazol-2-yl]amino]-1-piperidinyl]-ethyl]benzamide; mp. 171.7°C (intermediate 157).

In a similar manner there were also prepared:

15 2-(ethylamino)-N-[2-[4-[(1-(4-fluorophenyl)methyl)-1H-benzimidazol-2-yl]amino]-1-piperidinyl]ethyl]benzenamide; mp. 139.8°C (intermediate 158);
N-[2-[4-[(1-(4-fluorophenyl)methyl)-1H-benzimidazol-2-yl]amino]-1-piperidinyl]ethyl]-2-(methylamino)benzamide monohydrate;
20 mp. 147.8°C (intermediate 159);
2-amino-N-[2-[4-[(1-(2-furanyl)methyl)-1H-benzimidazol-2-yl]amino]-1-piperidinyl]ethyl]benzamide; mp. 167.3°C (intermediate 160);
N-[2-[4-[(1-(2-furanyl)methyl)-1H-benzimidazol-2-yl]amino]-1-piperidinyl]ethyl]-2-(methylamino)benzamide monohydrate; mp. 133.0°C
25 (intermediate 161);
2-amino-N-[4-[4-[(1-(2-furanyl)methyl)-1H-benzimidazol-2-yl]amino]-1-piperidinyl]butyl]benzamide; mp. 151.0°C (intermediate 162);
2-amino-N-[4-[4-[(1-(4-fluorophenyl)methyl)-1H-benzimidazol-2-yl]amino]-1-piperidinyl]butyl]benzamide; mp. 186.7°C (intermediate
30 163); and
2-amino-N-[2-[4-[(1-(4-fluorophenyl)methyl)-1H-benzimidazol-2-yl]amino]-1-piperidinyl]ethyl]-5-(methylthio)benzamide; mp. 184.6°C (intermediate 164).

Example 26

A mixture of 1.5 parts of 6-chloro-N⁴-[2-[4-[[1-[(4-fluoro-phenyl)methyl]-1H-benzimidazol-2-yl]amino]-1-piperidinyl]ethyl]-4,5-pyrimidinediamine, 3 parts of a solution of thiophene in ethanol 5 4%, 1 part of potassium acetate and 120 parts of methanol was hydrogenated at normal pressure and at room temperature with 1 part of palladium-on-charcoal catalyst 10%. After the calculated amount of hydrogen was taken up, the catalyst was filtered off and the filtrate was evaporated. The solid residue was taken up in water. 10 The solution was treated with ammonia. The product was extracted with trichloromethane. The organic layer was separated, dried, filtered and evaporated. The residue was crystallized from a mixture of 4-methyl-2-pentanone, yielding 1 part (72.4%) of N⁴-[2-[4-[[1-[(4-fluorophenyl)methyl]-1H-benzimidazol-2-yl]amino]-1-piperidinyl]ethyl]-4,5-pyrimidinediamine; mp. 207.7°C (intermediate 15 165).

Example 27

A mixture of 30 parts of 4-hydroxy-2-mercaptop-6-methyl-5-pyrimidineethanol, 25 parts of potassium carbonate, 270 parts of 20 N,N-dimethylacetamide and 75 parts of water was stirred at room temperature and 36 parts of 1,3-dibromopropane were added at once: temperature rises to 50°C. The whole was stirred overnight at room temperature. The reaction mixture was evaporated and water was added to the residue. The solid product was washed with water and dried in 25 vacuo at 100°C, yielding 21 parts (58%) of 3,4-dihydro-7-(2-hydroxyethyl)-8-methyl-2H,6H-pyrimido[2,1-b][1,3]thiazin-6-one; mp. 155°C (intermediate 166).

In a similar manner there was also prepared:
2,3-dihydro-6-(2-hydroxyethyl)-7-methyl-5H-thiazolo[3,2-a]pyrimidin-30 5-one; mp. 148.7°C (intermediate 167).

Example 28

A mixture of 20 parts of 3,4-dihydro-7-(2-hydroxyethyl)-8-methyl-2H,6H-pyrimido[2,1-b][1,3]thiazin-6-one, 50 parts of acetic acid and 180 parts of a hydrobromic acid solution 67% in acetic acid was 35 stirred and heated to reflux. Stirring was continued overnight at

reflux temperature. The reaction mixture was evaporated and the solid residue was triturated in 2-propanone. The product was filtered off and dried, yielding 24 parts (100%) of 7-(2-bromoethyl)-3,4-dihydro-8-methyl-2H,6H-pyrimido[2,1-b][1,3]thiazin-6-one 5 monohydrobromide; mp. 215°C (intermediate 168).

In a similar manner there was also prepared:

6-(2-bromoethyl)-2,3-dihydro-7-methyl-5H-thiazolo[3,2-a]pyrimidin-5-one monohydrobromide; mp. 237.2°C (intermediate 169).

Example 29

10 A mixture of 27 parts of ethyl 2-[(ethoxycarbonyl)methylamino]-benzoate, 16 parts of 2-aminoethanol and 90 parts of dimethylbenzene was stirred and refluxed overnight. The reaction mixture was cooled. The precipitated product was filtered off and crystallized from 2-propanol, yielding 4.5 parts (20%) of 3-(2-hydroxyethyl)-1-methyl-15 2,4(1H,3H)-quinazolinedione (intermediate 170).

A mixture of 4.5 parts of 3-(2-hydroxyethyl)-1-methyl-2,4(1H,3H)-quinazolinedione, 8 parts of thionyl chloride and 75 parts of trichloromethane was stirred and refluxed for 5 hours. The reaction mixture was evaporated, yielding 4.5 parts (95%) of 3-(2-chloro-20 ethyl)-1-methyl-2,4(1H,3H)-quinazolinedione as a residue (intermediate 171).

Example 30

A mixture of 50 parts of 2-thiazolamine, 76 parts of 3-acetyl-4,5-dihydro-2(3H)-furanone, 1.2 parts of concentrated hydrochloric 25 acid and 270 parts of methylbenzene was stirred and refluxed for 2 hours using a water-separator. The reaction mixture is cooled and 340 parts of phosphoryl chloride were added at a temperature between 20 and 30°C. The whole was heated slowly to 100-110°C and stirring was continued for 2 hours at this temperature. The reaction mixture 30 was evaporated and the residue was poured onto a mixture of crushed ice and ammonium hydroxide. The product was extracted with trichloromethane. The extract was dried, filtered and evaporated. The residue was purified by column chromatography over silica gel using a mixture of trichloromethane and methanol (95:5 by volume) as 35 eluent. The pure fractions were collected and the eluent was

evaporated. The residue was crystallized from a mixture of 2-propanol and 1,1'-oxybisethane, yielding 36 parts of 6-(2-chloroethyl)-7-methyl-5H-thiazolo[3,2-a]pyrimidin-5-one (intermediate 172).

Example 31

5 A mixture of 4.76 parts of 6-chloro-N⁴-methyl-4,5-pyridinediamine, 26.6 parts of 1,1,1-triethoxyethane and 30 parts of acetic acid anhydride was stirred and refluxed for 3 hours. The reaction mixture was evaporated. The residue was crystallized from a mixture of hexane and methylbenzene. The product was filtered off and dried, 10 yielding 5.3 parts (96.3%) of 6-chloro-8,9-dimethyl-9H-purine (intermediate 173).

Example 32

15 A mixture of 4.76 parts of 6-chloro-N⁴-methyl-4,5-pyrimidinediamine and 7.2 parts of urea was stirred and heated for 1 hour at 180°C. After cooling, the residue was suspended in water. The product was filtered off and dried, yielding 3.3 parts (60%) of 6-chloro-9-methyl-9H-purin-8-ol (intermediate 174).

Example 33

20 A mixture of 9.5 parts of 3-(2-chloroethyl)-2,6-dimethyl-4H-pyrido[1,2-a]-pyrimidin-4-one, 160 parts of methanol and 40 parts of 2-propanol saturated with hydrogen chloride was hydrogenated at normal pressure and at room temperature with 2 parts of palladium-on-charcoal catalyst 10%. After the calculated amount of hydrogen was taken up, the catalyst was filtered off over Hyflo and the 25 filtrate was evaporated, yielding 9.5 parts (86%) of 3-(2-chloroethyl)-6,7,8,9-tetrahydro-2,6-dimethyl-4H-pyrido[1,2-a]pyrimidin-4-one monohydrochloride (intermediate 175).

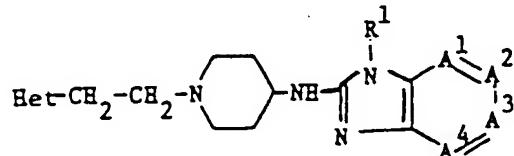
In a similar manner there were also prepared:

30 3-(2-chloroethyl)-6,7,8,9-tetrahydro-2,6,8-trimethyl-4H-pyrido[1,2-a]-pyrimidin-4-one monohydrochloride (intermediate 176);
3-(2-chloroethyl)-6,7,8,9-tetrahydro-2,7-dimethyl-4H-pyrido[1,2-a]pyrimidin-4-one monohydrochloride (intermediate 177).

B. Preparation of Final compounds.Example 34

A mixture of 5.52 parts of 6-(2-bromoethyl)-3,7-dimethyl-5H-thiazolo[3,2-a]pyrimidin-5-one monohydrobromide, 7.3 parts of 5 1-[(4-fluorophenyl)methyl]-N-(4-piperidinyl)-1H-benzimidazol-2-amine dihydrobromide, 6.4 parts of sodium carbonate and 135 parts of N,N-dimethylformamide was stirred and heated overnight at 70°C. The reaction mixture was poured onto water. The product was extracted with trichloromethane. The extract was dried, filtered and evaporated. The 10 residue was purified by column chromatography over silica gel using a mixture of trichloromethane and methanol (94:6 by volume), saturated with ammonia, as eluent. The pure fractions were collected and the eluent was evaporated. The residue was crystallized from acetonitrile, yielding 5 parts (62.8%) of 6-[2-[4-[(1-[(4-fluorophenyl)methyl]-15 1H-benzimidazol-2-yl]amino]-1-piperidinyl]ethyl]-3,7-dimethyl-5H-thiazolo[3,2-a]pyrimidin-5-one; mp. 141.0°C (compound 1).

Following the same procedure and using equivalent amounts of the appropriate starting materials, there were also prepared:



Comp. No.	Het	R ¹	A ¹ =A ² -A ³ =A ⁴	base or salt form	mp. °C
2		4-F-C ₆ H ₄ -CH ₂ -	-CH=CH-CH=CH-	H ₂ O	222.6
3		4-F-C ₆ H ₄ -CH ₂ -	-CH=CH-CH=CH-	base	190.7

Comp. No.	Het	R ¹	A ¹ =A ² -A ³ =A ⁴	base or salt form	mp. °C
5 4		4-F-C ₆ H ₄ -CH ₂ -	-CH=CH-CH=CH-	3HCl. 2H ₂ O	237.3
10 5		2-furanyl- methyl-	-CH=CH-CH=CH-	base	108.1
15 6		2-furanyl- methyl-	-N-CH-CH=CH-	base	202.4
20 7		4-F-C ₆ H ₄ -CH ₂ -	-N-CH-CH=CH-	base	99.7
25 8		4-F-C ₆ H ₄ -CH ₂ -	-CH=CH-CH=CH-	base	222.7
30 9		2-furanyl- methyl-	-CH=CH-CH=CH-	H ₂ O	129.1
35 10		2-furanyl- methyl-	-N-CH-CH=CH-	base	127.4

Comp. No.	Het	R ¹	A ¹ =A ² -A ³ =A ⁴	base or salt form	mp. °C
5 11		2-furanyl- methyl	-CH=CH-CH=CH-	base	258.0
10 12		4-F-C ₆ H ₄ -CH ₂ -	-N=CH-CH=CH-	2HCl H ₂ O	196.1
15 13		2-furanyl- methyl	-CH=CH-CH=CH-	base	107.4
20 14		2-furanyl- methyl	-N=CH-CH=CH-	base	161.2
25 15		4-F-C ₆ H ₄ -CH ₂ -	-CH=CH-CH=CH-	3HCl 2H ₂ O	229.1
30 16		4-F-C ₆ H ₄ -CH ₂ -	-N=CH-CH=CH-	3HCl	239.3
35 17		4-F-C ₆ H ₄ -CH ₂ -	-CH=CH-CH=CH-	base	241.1

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Comp. No.	Het	R ¹	A ¹ -A ² -A ³ -A ⁴	base or salt form	mp. °C
5 18		2-furanyl- methyl	-CH=CH-CH=CH-	base	224.5
10 19		4-thiazolyl- methyl	-CH=CH-CH=CH-	base	167.1
15 20		2-furanyl- methyl	-N=CH-CH=CH-	base	221.0
20 21		2-furanyl- methyl	-N=CH-CH=CH-	base	219.7

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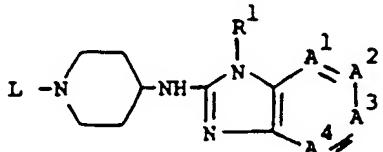
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Example 35

A mixture of 3.34 parts of 3-(2-chloroethyl)-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one, 6 parts of 3-(4-fluorophenylmethyl)-N-(4-piperidinyl)-3H-imidazo[4,5-b]pyridin-2-amine dihydrochloride, 4.85 parts of sodium carbonate, 0.1 parts of potassium iodide and 135 parts of N,N-dimethylformamide was stirred and heated overnight at 70°C. The reaction mixture was poured onto water. The product was extracted with trichloromethane. The extract was dried, filtered and evaporated. The residue was purified by column-chromatography over 10 silica gel using a mixture of trichloromethane and methanol, saturated with ammonia, (96:4 by volume) as eluent. The pure fractions were collected and the eluent was evaporated. The residue was crystallized from acetonitrile, yielding 4 parts (60%) of 3-[2-[4-[(3-[(4-fluorophenyl)methyl]-3H-imidazo[4,5-b]pyridin-2-yl]amino]-1-piperidinyl]ethyl]-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one dihydrochloride; mp. 195.7°C (compound 22).

In a similar manner there were also prepared:

20



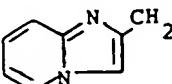
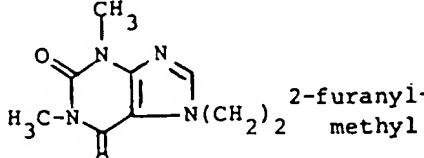
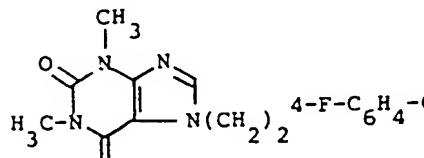
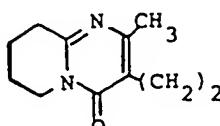
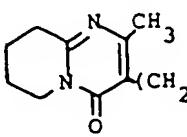
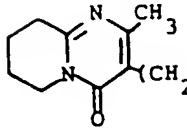
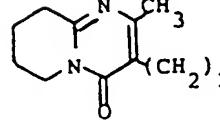
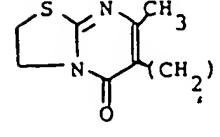
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Comp. No.	L	R ¹	A ¹ =A ² =A ³ =A ⁴	base or salt form	mp. °C
23		4-F-C ₆ H ₄ -CH ₂ -	-CH=CH-CH=CH-	2HCl H ₂ O	226.9
24		2-furanyl-methyl	-CH=CH-CH=CH-	base	238.4

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Comp. No.	L	R ¹	¹ A-A ² -A ³ -A ⁴	base or salt form	mp. °C
5 25		4-F-C6H4-CH2-	-N=CH-CH=CH-	H2O	251.6
10 26		2-furanyl- methyl	-N=CH-CH=CH-	base	231.7
15 27		4-F-C6H4-CH2-	-CH=CH-CH=CH-	base	115.1
20 28		2-furanyl- methyl	-N=CH-CH=CH-	base	186.4
25 29		4-F-C6H4-CH2-	-CH=CH-CH=CH-	base	245.3
30 30		2-furanyl- methyl	-CH=CH-CH=CH-	base	250.7
35 31		2-furanyl- methyl	-CH=CH-CH=CH-	base	103.6
35 32		2-furanyl- methyl	-N=CH-CH=CH-	base	234.0

Comp. No.	L	R ¹	A ¹ =A ² -A ³ =A ⁴	base or salt form	mp. °C
5 33		4-F-C ₆ H ₄ -CH ₂ -	-CH=CH-CH=CH-	2HCl H ₂ O	207.1
10 34		2-furanyl- methyl	-CH=CH-CH=CH-	base	217.4
15 35		2-furanyl- methyl	-N=CH-CH=CH-	base	195.0
20 36		4-F-C ₆ H ₄ -CH ₂ -	-N=CH-CH=CH-	2HCl	291.2
25 37		4-F-C ₆ H ₄ -CH ₂ -	-N=CH-CH=CH-	H ₂ O	236.1
30 38		4-F-C ₆ H ₄ -CH ₂ -	-N=CH-CH=CH-	2HCl	259.6
35 39		2-furanyl- methyl	-CH=CH-CH=CH-	base	192.0
40		4-F-C ₆ H ₄ -CH ₂ -	-CH=CH-CH=CH-	base	234.8

Comp. No.	L	R ¹	$A^1 = A^2 - A^3 = A^4$	base or salt form	mp. °C
5 41		4-F-C ₆ H ₄ -CH ₂ -	-CH=CH-CH=CH-	base	196.6
10 42		2-furanyl- methyl	-N=CH-CH=CH-	base	195.3
15 43		4-F-C ₆ H ₄ -CH ₂ -	-N=CH-CH=CH-	2HBr H ₂ O	246.6
20 44		2-furanyl- methyl	-CH=CH-CH=CH-	3HCl 3H ₂ O	211.2
25 45		4-F-C ₆ H ₄ -CH ₂ -	-CH=CH-CH=CH-	3HCl 2H ₂ O	223.2
30 46		4-F-C ₆ H ₄ -CH ₂ -	-N=CH-CH=CH-	base	204.8
35 47		2-furanyl- methyl	-N=CH-CH=CH-	base	177.8
35 48		2-furanyl- methyl	-N=CH-CH=CH-	base	153.8

Comp. No.	L	R ¹	A ¹ =A ² -A ³ =A ⁴	base or salt form	mp. °C
5 49		4-F-C ₆ H ₄ -CH ₂ -	-CH=CH-CH=CH-	base	187.1
10 50		4-F-C ₆ H ₄ -CH ₂ -	-CH=CH-C(=CH-CH ₃)-	base	168.7
15 51		3-pyridinyl- methyl	-CH=CH-CH=CH-	base	205.1
20 52		2-thienyl- methyl	-CH=CH-CH=CH-	base	219.4
25 53		4-F-C ₆ H ₄ -CH ₂	-CH=CH-N=CH-	base	222.3
30 54		2-furanyl- methyl	-N=CH-CH=CH-	base	175.6
35 55		2-pyridinyl- methyl	-N=CH-CH=CH-	base	207.3
35 56		2-pyridinyl- methyl	-CH=CH-CH=CH-	base	193.3

Comp. No.	L	R ¹	A ¹ =A ² -A ³ =A ⁴	base or salt form	mp. °C
5 57		2-pyridinyl- methyl	-CH=CH-CH=CH-	base	193.8
10 58		2-furanyl- methyl	-N=CH-CH=CH-	base	208.4
15 59		2-thienyl- methyl	-CH=CH-CH=CH-	base	214.0
20 60		4-F-C ₆ H ₄ -CH ₂ -	-CH=CH-N=CH-	base	230.5
25 61		4-F-C ₆ H ₄ -CH ₂ -	-N=CH-CH=CH-	base	166.0
30 62		4-thiazolyl- methyl	-CH=CH-CH=CH-	base	158.8
30 63		2-furanyl- methyl	-N=CH-CH=CH-	base	86.2

Comp. No.	L	R ¹	A ¹ =A ² -A ³ =A ⁴	base or salt form	mp. °C
5 64		4-thiazolyl- methyl	-CH=CH-CH=CH-	base	239.5
10 65		3-pyridinyl- methyl	-CH=CH-CH=CH-	base	235.1
15 66		2-pyridinyl- methyl	-CH=CH-CH=CH-	base	238.8
20 67		2-pyridinyl- methyl	-N=CH-CH=CH-	base	240.2

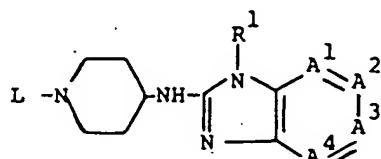
Example 36

A mixture of 3.15 parts of 3-(2-chloroethyl)-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one, 8.26 parts of N-(4-piperidinyl)-1-(2-pyrazinylmethyl)-1H-benzimidazol-2-amine trihydrobromide, 6.4 parts of sodium carbonate, 0.1 parts of potassium iodide and 90 parts of N,N-dimethylacetamide was stirred and heated overnight at 80°C. The reaction mixture was poured into water. The product was extracted with trichloromethane. The extract was dried, filtered and evaporated. The residue was purified by column chromatography over silica gel using a mixture of trichloromethane and methanol, saturated with ammonia, (96:4 by volume) as eluent. The pure fractions were collected and the eluent was evaporated. The residue was crystallized from acetonitrile. The product was filtered off and dried, yielding 5 parts, (67.4%) of 2-methyl-3-[2-(4-[(1-(2-pyrazinyl-

35

methyl)-1H-benzimidazol-2-yl]amino]-1-piperidinyl]ethyl]-4H-pyrido-[1,2-a]pyrimidin-4-one; mp. 204.4°C (compound 68).

In a similar manner there were also prepared:



Comp. No.	L	R ¹	¹ A=A ² -A ³ =A ⁴	base or salt form	mp. °C
69		4-Cl-C ₆ H ₄ -CH ₂ - -CH=CH-CH=CH-	base	208.0	
70		4-F-C ₆ H ₄ -CH ₂ - -CH=CF-CF=CH-	base	132.3	
71		CH ₃ -CH ₂ - -CH=CH-CH=CH-	2HCl 1/2H ₂ O	225.9	
72		H -CH=CH-CH=CH-	base	238.5	
73		cyclohexyl -CH=CH-CH=CH-	base	156.2	
74		2-furanyl- methyl -N=CH-CH=CH-	H ₂ O	153.3	
75		2-furanyl- methyl -N=CH-CH=CH-	base	175.8	

Comp. No.	L	R ¹	A ¹ =A ² -A ³ =A ⁴	base or salt form	mp. °C
5 76		2-furanyl-methyl	-N=CH-CH=CH-	H ₂ O	218.3
10 77		2-furanyl-methyl	-N=CH-CH=CH-	H ₂ O	140.6
15 78		4-F-C ₆ H ₄ -CH ₂ -	-CH=CH-C(=CH-CH ₃)-	base	192.8
20 79		4-F-C ₆ H ₄ -CH ₂ -	-CH=N-CH=CH-	3 HCl 2 H ₂ O	251.6
25 80		2-thienyl-methyl	-CH=CH-CH=CH-	base	243.4
30 81		2-thienyl-methyl	-N=CH-CH=CH-	base	-
35 82		3-furanyl-methyl	-N=CH-CH=CH-	base	-
30 83		5-methyl-2-furanyl-methyl	-N=CH-CH=CH-	base	-
35 84		2-thienyl-methyl	-N=CH-CH=CH-	base	-

Comp. No.	L	R ¹	A ¹ =A ² -A ³ =A ⁴	base or salt form	mp. °C
5 85		3-furanyl- methyl	-N=CH-CH=CH-	base	-
10 86		5-methyl- 2-furanyl- methyl	-N=CH-CH=CH-	base	-
15 87		2-thienyl- methyl	-N=CH-CH=CH-	base	-
20 88		3-furanyl- methyl	-N=CH-CH=CH-	base	-
25 89		5-methyl- 2-furanyl- methyl	-N=CH-CH=CH-	base	-

In a similar manner there were also prepared:

3-[2-[4-[(1-[(4-fluorophenyl)methyl]-1H-benzimidazol-2-yl](phenylmethyl)amino]-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one (E)-2-butenedioate(1:1); mp. 186.4°C

25 (compound 90);

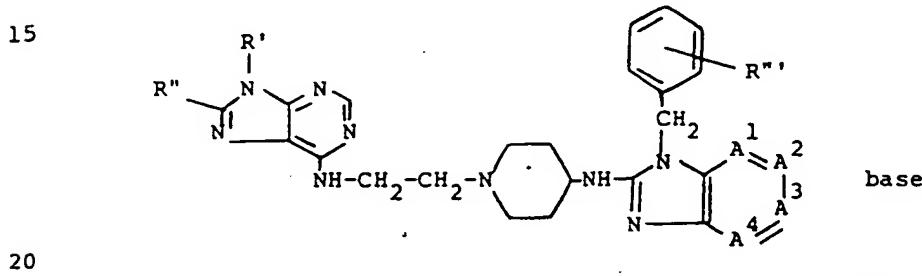
3-[2-[4-[(1-[(4-fluorophenyl)methyl]-1H-benzimidazol-2-yl)methylamino]-1-piperidinyl]ethyl]-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one trihydrochloride; mp. 244.7°C (compound 91); and

30 cis-3-[2-[4-[(1-[(4-fluorophenyl)methyl]-1H-benzimidazol-2-yl)amino]-3-methyl-1-piperidinyl]ethyl]-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one; mp. 160.6°C (compound 92).

Example 37

A mixture of 2 parts of 6-chloro-9H-purine-9-ethanol, 3.7 parts of N-[1-(2-aminoethyl)-4-piperidinyl]-1-[(4-fluorophenyl)methyl]-1H-benzimidazol-2-amine, 1.06 parts of sodium carbonate and 45 parts of 5 N;N-dimethylacetamide was stirred and heated for 3 hours at 130°C. The reaction mixture was poured into water and the product was extracted with 4-methyl-2-pentanone. The extract was dried, filtered and evaporated. The residue was crystallized from acetonitrile. The product was filtered off and dried, yielding 2.8 parts (53%) of 10 6-[[2-[4-[[1-[(4-fluorophenyl)methyl]-1H-benzimidazol-2-yl]amino]-1-piperidinyl]ethyl]amino]-9H-purine-9-ethanol; mp. 168.7°C (compound 93).

In a similar manner there were also prepared:



Comp. No.	R'	R''	R'''	$A^1 = A^2 = A^3 = A^4$	mp. °C
94	CH ₃	H	4-fluoro	-CH=CH-CH=CH-	188.0
95	C ₆ H ₅ CH ₂	H	4-fluoro	-CH=CH-CH=CH-	145.5
96	CH ₃	CH ₃	4-fluoro	-CH=CH-CH=CH-	211.7
97	H	H	4-fluoro	-CH=CH-CH=CH-	151.4
98	CH ₃	OH	4-fluoro	-CH=CH-CH=CH-	257.1
99	CH ₃	H	3-CH ₃	-CH=CH-CH=CH-	188.9
100	CH ₃	H	H	-CH=CH-CH=CH-	207.5
101	CH ₃	H	4-fluoro	-CH=C-CH=CH- OCH ₃	194.5
102	CH ₃	H	4-fluoro	-CH=CH-C=CH- OH	186.1

35

Example 38

A mixture of 2.8 parts of 2-(methylthio)thiazolo[5,4-b]pyridine and 5.5 parts of N-[1-(2-aminoethyl)-4-piperidinyl]-1-[(4-fluorophenyl)methyl]-1H-benzimidazol-2-amine was stirred for 24 hours at 5 140°C. The reaction mixture was purified by column chromatography over silica gel using a mixture of trichloromethane and methanol, saturated with ammonia, (97:3 by volume) as eluent. The pure fractions were collected and the eluent was evaporated. The residue was crystallized from acetonitrile. The product was filtered off and 10 dried, yielding 1.9 parts (25%) of N-[2-[4-[(1-[(4-fluorophenyl)methyl]-1H-benzimidazol-2-yl]amino]-1-piperidinyl]ethyl]thiazolo-[5,4-b]pyridin-2-amine; mp. 203.5°C (compound 103).

In a similar manner there was also prepared:

N-[2-[4-[(1-[(4-fluorophenyl)methyl]-1H-benzimidazol-2-yl]amino]-1-piperidinyl]ethyl]thiazolo[4,5-c]pyridin-2-amine; mp. 192.6°C (compound 104).

Example 39

A mixture of 2.5 parts of thiazolo[5,4-b]pyridine-2-thiol, 1 part of a sodium hydride dispersion 50% and 45 parts of N,N-dimethylformamide was stirred for 1 hour. Then there was added a solution of 20 6.9 parts of N-[1-(2-chloroethyl)-4-piperidinyl]-1-(4-fluorophenylmethyl)-1H-benzimidazol-2-amine in 45 parts of N,N-dimethylformamide. The whole was stirred overnight. Water was added dropwise. The product was extracted with 4-methyl-2-pentanone. The extract was 25 dried, filtered and evaporated. The residue was purified by column chromatography over silica gel using a mixture of trichloromethane and methanol, saturated with ammonia, (95:5 by volume) as eluent. The pure fractions were collected and the eluent was evaporated. The residue was crystallized from acetonitrile. The product was filtered 30 off and dried, yielding 0.5 parts (6.4%) of 1-[(4-fluorophenyl)methyl]-N-[1-[2-(thiazolo[5,4-b]pyridin-2-ylthio)ethyl]-4-piperidinyl]-1H-benzimidazol-2-amine; mp. 159.9°C (compound 105).

Example 40

To a stirred and cooled (0°C) mixture of 3.8 parts of poly(oxy-

methylene) 37%, 15.5 parts of 1-[(4-fluorophenyl)methyl]-N-
(4-piperidinyl)-1H-benzimidazol-2-amine and 7 parts of glacial
acetic acid were added 6.5 parts of 2-methylimidazo[1,2-a]pyridine
under nitrogen atmosphere. The whole was heated slowly to 50°C and
5 stirring was continued at 50°C for 2 hours. After stirring was
continued overnight at room temperature, the reaction mixture was
poured into water and the whole was made alkaline with sodium
hydroxide. The product was extracted with dichloromethane. The
extract was dried, filtered and evaporated. The residue was purified
10 by column chromatography over silica gel using a mixture of
trichloromethane and methanol, saturated with ammonia, (96:4 by
volume) as eluent. The pure fractions were collected and the eluent
was evaporated. The residue was crystallized from acetonitrile. The
product was filtered off and dried, yielding 6.7 parts (30%) of
15 1-[(4-fluorophenyl)methyl]-N-[1-[(2-methylimidazo[1,2-a]pyridin-3-
yl)methyl]-4-piperidinyl]-1H-benzimidazol-2-amine; mp. 198.1°C
(compound 106).

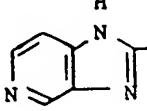
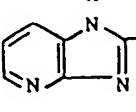
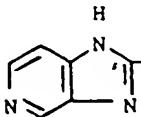
Example 41

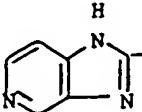
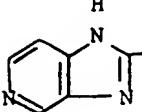
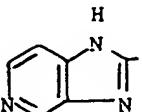
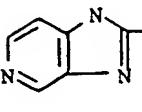
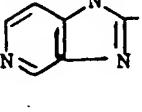
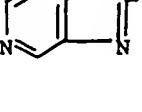
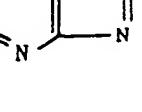
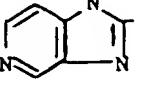
To a stirred mixture of 5.3 parts of 4-[1-(4-fluorophenylmethyl)-
20 1H-benzimidazol-2-ylamino]-1-piperidineethanol dihydrochloride, 2.8
parts of a sodium hydride dispersion 50% and 90 parts of N,N-di-
methylformamide were added 2.55 parts of 2-(methylsulfonyl)thiazolo-
[5,4-b]pyridine. The whole was stirred for 2 hours. The reaction
mixture was poured into water. The product was extracted with
25 4-methyl-2-pentanone. The extract was dried, filtered and
evaporated. The residue was purified by column chromatography over
silica gel using a mixture of trichloromethane, hexane and methanol
(45:45:10 by volume) as eluent. The pure fractions were collected
and the eluent was evaporated. The residue was crystallized from
30 acetonitrile. The product was filtered off and dried, yielding 0.9
parts (15%) of 1-[(4-fluorophenyl)methyl]-N-[1-[2-[(thiazolo[5,4-b]-
pyridin-2-yl)oxy]ethyl]-4-piperidinyl]-1H-benzimidazol-2-amine;
mp. 151.0°C (compound 107).

Example 42

A mixture of 8 parts of N-[2-[4-[[1-[(4-fluorophenyl)methyl]-1H-benzimidazol-2-yl]amino]-1-piperidinyl]ethyl]-N'-[4-(methylamino)-3-pyridinyl]thiourea, 15 parts of mercury(II)oxide, 0.1 parts of sulfur and 120 parts of ethanol was stirred and refluxed for 3 hours. After the addition of another 15 parts of mercury(II)oxide, stirring at reflux was continued for 2 hours. The reaction mixture was filtered over Hyflo and the filtrate was evaporated. The residue was purified by column chromatography over silica gel using a mixture of trichloromethane and methanol saturated with ammonia (95:5 by volume) as eluent. The pure fractions were collected and the eluent was evaporated. The residue was crystallized from acetonitrile. The product was filtered off and dried, yielding 4.4 parts (59%) of N-[2-[4-[[1-[(4-fluorophenyl)methyl]-1H-benzimidazol-2-yl]amino]-1-piperidinyl]ethyl]-1-methyl-1H-imidazo[4,5-c]pyridin-2-amine monohydrate; mp. 144.6°C (compound 108).

In a similar manner there were also prepared:

Comp. No.	Het	R ¹	A ¹ =A ² -A ³ =A ⁴	base or salt form	mp. °C
109		4-F-C ₆ H ₄ -CH ₂ -	-CH=CH-CH=CH-	base	250.5
110		4-F-C ₆ H ₄ -CH ₂ -	-CH=CH-CH=CH-	base	259.3
111		2-furanyl-methyl	-CH=CH-CH=CH-	base	229.8

Comp. No.	Het	R ¹	A ¹ =A ² -A ³ =A ⁴	base or salt form	mp. °C
5 112		4-F-C ₆ H ₄ -CH ₂ -	-CH=CH-CH=N-	base	276.7
10 113		2-pyridinyl methyl	-N=CH-CH=CH-	base	243.0
15 114		4-F-C ₆ H ₄ -CH ₂ -	-N=CH-CH=CH-	4(COOH) ₂	238.8
20 115		2-pyridinyl methyl	-CH=CH-CH=CH-	base	233.0
25 116		phenyl	-CH=CH-CH=CH-	base	212.6
30 117		2-thienyl- methyl	-CH=CH-CH=CH-	base	232.6
35 118		4-F-C ₆ H ₄ -CH ₂ -	-CH=CH-CH=CH-	base	265.6
35 119		2-furyl- methyl	-N=CH-CH=CH-	(E) (CH-COOH) ₂ (1:3).H ₂ O ₂	169.0

Comp. No.	Het	R ¹	A ¹ =A ² -A ³ =A ⁴	base or salt form	mp. °C
5 120		4-F-C ₆ H ₄ -CH ₂ -	-CH=CH-CH=CH-	base	219.9

Example 43

A mixture of 18 parts of N-(4-amino-3-pyridinyl)-N'-[4-[4-[(1-10 [(4-fluorophenyl)methyl]-1H-benzimidazol-2-yl]amino]-1-piperidinyl]-butyl]thiourea, 7 parts of mercury(II)oxide, 1 part of sulfur and 180 parts of tetrahydrofuran was stirred and refluxed for 5 hours. The reaction mixture was filtered hot over Hyflo and the filtrate was evaporated. The residue was purified by column chromatography 15 over silica gel using a mixture of trichloromethane and methanol saturated with ammonia, (90:10 by volume) as eluent. The pure fractions were collected and the eluent was evaporated. The residue was crystallized from a mixture of tetrahydrofuran and trichloromethane, yielding 5 parts (29%) of N-[4-[4-[(1-[(4-fluorophenyl)-20 methyl]-1H-benzimidazol-2-yl]amino]-1-piperidinyl]butyl]-1H-imidazo-[4,5-c]pyridin-2-amine; mp. 228.2°C (compound 121).

In a similar manner there were also prepared:

N-[3-[4-[(1-[(4-fluorophenyl)methyl]-1H-benzimidazol-2-yl]amino]-1-piperidinyl]propyl]-1H-imidazo[4,5-c]pyridin-2-amine ethane-25 dioate(2:7); mp. 220.4°C (compound 122); and N-[2-[4-[(1-[(4-fluorophenyl)methyl]-1H-benzimidazol-2-yl]amino]-1-piperidinyl]ethyl]-3-methyl-3H-imidazo[4,5-c]pyridin-2-amine ethane-dioate(1:3) monohydrate; mp. 242.3°C (compound 123).

Example 44

30 To a stirred mixture of 7.7 parts of 2-(ethylamino)-N-[2-[4-[(1-[(4-fluorophenyl)methyl]-1H-benzimidazol-2-yl]amino]-1-piperidinyl]-ethyl]benzamide, 2 parts of N,N-diethylethanamine and 90 parts of tetrahydrofuran were added dropwise 1.6 parts of ethyl carbono-

chloride. Upon completion, stirring was continued for 1 hour at room temperature. The reaction mixture was evaporated and 4-methyl-2-pentanone was added to the residue. The organic phase was washed with water, dried, filtered and evaporated. The residue was purified 5 by column chromatography over silica gel using a mixture of trichloromethane and methanol (90:10 by volume) as eluent. The pure fractions were collected and the eluent was evaporated. The residue was further purified by HPLC using a mixture of methylbenzene and ethanol (90:10 by volume) as eluent. The pure fraction was collected 10 and the eluent was evaporated. The residue was crystallized from acetonitrile, yielding 2.2 parts (25%) of ethyl [1-[2-[1-ethyl-1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl]ethyl]-4-piperidinyl]-[1-[(4-fluorophenyl)methyl]-1H-benzimidazol-2-yl]carbamate; mp. 160.3°C (compound 124).

15 Example 45

To a stirred mixture of 4 parts of 2-(ethylamino)-N-[2-[4-[(1-(4-fluorophenyl)methyl)-1H-benzimidazol-2-yl]amino]-1-piperidinyl]-ethyl]benzamide, 1.06 parts of sodium carbonate and 65 parts of dichloromethane was added dropwise a solution of 2 parts of methyl 20 carbonochloride in dichloromethane. Upon completion, stirring was continued overnight at reflux temperature. Water was added and the product was extracted with dichloromethane. The extract was dried, filtered and evaporated. The residue was purified by column chromatography over silica gel using a mixture of trichloromethane 25 and methanol (90:10 by volume) as eluent. The pure fractions were collected and the eluent was evaporated. The residue was converted into the hydrochloride salt in acetonitrile and 2-propanol. The salt was filtered off and dried, yielding 1.8 parts of 1-ethyl-3-[2-[4-[(1-(4-fluorophenyl)methyl)-1H-benzimidazol-2-yl]amino]-1-piperi-30 dinyl]ethyl]-2,4(1H,3H)-quinazolinedione dihydrochloride; mp. +260°C (compound 125).

Example 46

A mixture of 6 parts of 2-amino-N-[2-[4-[(1-(4-fluorophenyl)-methyl)-1H-benzimidazol-2-yl]amino]-1-piperidinyl]ethyl]-5-(methyl-35 thio)benzamide, 1.78 parts of 1,1'-carbonylbis[1H-imidazole] and 90

parts of tetrahydrofuran was stirred and refluxed overnight. The reaction mixture was evaporated. The residue was crystallized from acetonitrile. The product was filtered off and dried, yielding 5.2 parts (85%) of 3-[2-[4-[(1-[(4-fluorophenyl)methyl]-1H-benzimidazol-2-yl]amino]-1-piperidinyl]ethyl]-6-(methylthio)-2,4(1H,3H)-quinazolinedione; mp. 238°C (compound 126).

In a similar manner there were also prepared:

3-[4-[4-[(1-[(4-fluorophenyl)methyl]-1H-benzimidazol-2-yl]amino]-1-piperidinyl]butyl]-2,4(1H,3H)-quinazolinedione; mp. 212.6°C (compound 127); and
3-[4-[4-[(1-(2-furanyl)methyl)-1H-benzimidazol-2-yl]amino]-1-piperidinyl]-butyl]-2,4(1H,3H)-quinazolinedione; mp. 194.3°C (compound 128).

Example 47

To a stirred mixture of 4.7 parts of N-[2-[4-[(1-(2-furanyl)methyl)-1H-benzimidazol-2-yl]amino]-1-piperidinyl]ethyl]-2-(methylamino)-benzamide, 2.02 parts of N,N-diethylethanamine and 195 parts of dichloromethane was added dropwise a solution of 1.14 parts of carbonothioic dichloride in dichloromethane. Upon completion, stirring was continued overnight at room temperature. The reaction mixture was poured into water. The layers were separated. The organic layer was dried, filtered and evaporated. The residue was purified by column chromatography over silica gel using a mixture of trichloromethane and methanol, saturated with ammonia, (96:4 by volume) as eluent. The pure fractions were collected and the eluent was evaporated. The residue was crystallized from acetonitrile, yielding 1.4 parts (27.5%) of 3-[2-[4-[(1-(2-furanyl)methyl)-1H-benzimidazol-2-yl]amino]-1-piperidinyl]ethyl]-2,3-dihydro-1-methyl-2-thioxo-4(1H)-quinazolinone; mp. 188.4°C (compound 129).
In a similar manner there was also prepared:
3-[2-[4-[(1-[(4-fluorophenyl)methyl]-1H-benzimidazol-2-yl]amino]-1-piperidinyl]ethyl]-2,3-dihydro-1-methyl-2-thioxo-4(1H)-quinazolinone; mp. 215.8°C (compound 130).

Example 48

To a stirred solution of 10.9 parts of N-[1-(2-aminoethyl)-4-piperidinyl]-1-(4-fluorophenylmethyl)-1H-benzimidazol-2-amine in 150 parts of tetrahydrofuran was added dropwise a solution of 6 parts of 5 methyl 2-isothiocyanatobenzoate in 30 parts of tetrahydrofuran at room temperature: slightly exothermic reaction, the temperature rose to 30°C. Upon completion, stirring at room temperature was continued for one hour. The reaction mixture was evaporated. The residue was stirred in trichloromethane. The formed precipitate was filtered off 10 and crystallized from 2-propanone. The product was filtered off and dried, yielding 5.2 parts of 3-[2-[4-[1-(4-fluorophenylmethyl)-1H-benzimidazol-2-yl]amino]-1-piperidinyl]ethyl]-1,2-dihydro-2-thioxo-4(3H)-quinazolinone; mp. 198.5°C (compound 131)

In a similar manner there were also prepared:

15 3-[2-[4-[1-(2-furanyl)ethyl]-1H-benzimidazol-2-yl]amino]-1-piperidinyl]ethyl]-2,3-dihydro-2-thioxo-4(1H)-quinazolinone; mp. 146.0°C (compound 132);
3-[2-[4-[1-[(4-fluorophenyl)methyl]-1H-benzimidazol-2-yl]amino]-1-piperidinyl]ethyl]-2,3-dihydro-6-methyl-2-thioxothieno[2,3-d]-20 pyrimidin-4(1H)-one; mp. 236.4°C (compound 133); and
3-[2-[4-[1-(2-furanyl)ethyl]-1H-benzimidazol-2-yl]amino]-1-piperidinyl]ethyl]-2,3-dihydro-6-methyl-2-thioxothieno[2,3-d]pyrimidin-4(1H)-one monohydrate; mp. 214.5°C (compound 134).

Example 49

25 To a stirred mixture of 4.1 parts of 3-[2-[4-[1-[(4-fluorophenyl)methyl]-1H-benzimidazol-2-yl]amino]-1-piperidinyl]ethyl]-2,3-dihydro-6-methyl-2-thioxothieno[2,3-d]pyrimidin-4(1H)-one, 5.6 parts of potassium hydroxide, 81 parts of ethanol and 8 parts of water were added dropwise 60 parts of a hydrogen peroxide solution 3%. The 30 whole was stirred overnight. The reaction mixture was evaporated. The residue was purified by column chromatography over silica gel using a mixture of trichloromethane and methanol (90:10 by volume) as eluent. The pure fractions were collected and the eluent was evaporated. The residue was crystallized from 2-propanone. The 35 product was filtered off and dried, yielding 2.2 parts (55%) of

3-[2-[4-[(1-[(4-fluorophenyl)methyl]-1H-benzimidazol-2-yl]amino]-1-piperidinyl]ethyl]-6-methylthieno[2,3-d]pyrimidine-2,4(1H,3H)-dione; mp. 187.6°C (compound 135).

In a similar manner there was also prepared:

5 3-[2-[4-[(1-(2-furanyl)methyl)-1H-benzimidazol-2-yl]amino]-1-piperidinyl]ethyl]-6-methylthieno[2,3-d]pyrimidine-2,4(1H,3H)-dione; mp. 151.7°C (compound 136).

Example 50

10 A mixture of 4.86 parts of 2-amino-N-[2-[4-[(1-[(4-fluorophenyl)methyl]-1H-benzimidazol-2-yl]amino]-1-piperidinyl]ethyl]benzamide, 1.4 parts of formic acid and 45 parts of methylbenzene was stirred and refluxed overnight. The reaction mixture was evaporated and the residue was taken up in trichloromethane, water and ammonium hydroxide. The organic phase was separated, dried, filtered and evaporated. The residue was crystallized from acetonitrile, yielding 15 3.6 parts (73%) of 3-[2-[4-[(1-[(4-fluorophenyl)methyl]-1H-benzimidazol-2-yl]amino]-1-piperidinyl]ethyl]-4(3H)-quinazolinone; mp. 190.6°C (compound 137).

Example 51

20 A mixture of 3.7 parts of 2-amino-5-(methylthio)benzoic acid and 8.9 parts of N-[2-[4-[(1-[(4-fluorophenyl)methyl]-1H-benzimidazol-2-yl]amino]-1-piperidinyl]ethyl]formamide was stirred for 5 hours at 150-160°C. The whole was purified by column chromatography over silica gel using a mixture of trichloromethane and methanol, 25 saturated with ammonia, (95:5 by volume) as eluent. The pure fractions were collected and the eluent was evaporated. The residue was crystallized from a mixture of 1,1'-oxybisethane and acetonitrile. The product was filtered off and dried, yielding 4.5 parts (41.5%) of 3-[2-[4-[(1-[(4-fluorophenyl)methyl]-1H-benzimidazol-2-yl]amino]-1-piperidinyl]ethyl]-6-(methylthio)-4(3H)-quinazolinone; mp. 101.4°C (compound 138).

Example 52

35 A mixture of 3 parts of 2-amino-N-[2-[4-[(1-[(4-fluorophenyl)methyl]-1H-benzimidazol-2-yl]amino]-1-piperidinyl]ethyl]benzenamide, 20 parts of acetic acid anhydride and 40 parts of water was stirred

overnight at 120°C. The reaction mixture was cooled and ammonium hydroxide was added. The product was extracted with 4-methyl-2-pentanone. The extract was dried, filtered and evaporated. The residue was purified by column chromatography over silica gel using 5 a mixture of trichloromethane and methanol (90:10 by volume) as eluent. The pure fractions were collected and the eluent was evaporated. The residue was crystallized from acetonitrile, yielding 2 parts (67%) of 3-[2-[4-[(1-[(4-fluorophenyl)methyl]-1H-benzimidazol-2-yl]amino]-1-piperidinyl]ethyl]-2-methyl-4(3H)-quinazolin-10 none; mp. 185.5°C (compound 139).

In a similar manner there was also prepared:
3-[2-[4-[(1-(2-furanyl)methyl)-1H-benzimidazol-2-yl]amino]-1-piperidinyl]ethyl]-2-methyl-4(3H)-quinazolinone; mp. 155.7°C; (compound 140).

Example 53

15 A mixture of 8.85 parts of 2-amino-N-[2-[4-[(1-[(4-fluorophenyl)methyl]-1H-benzimidazol-2-yl]amino]-1-piperidinyl]ethyl]benzenamide, 1.9 parts of ethyl 2-propynoate and 40 parts of ethanol was stirred and refluxed for 24 hours. The reaction mixture was evaporated. The residue was purified by column chromatography over silica gel using 20 a mixture of trichloromethane and methanol, saturated with ammonia, (95:5 by volume) as eluent. The pure fractions were collected and the eluent was evaporated. The residue was converted into the (E)-2-butenedioate salt in ethanol. The salt was filtered off and dried, yielding 5.1 parts of ethyl 3-[2-[4-[(1-[(4-fluorophenyl)methyl]-1H-benzimidazol-2-yl]amino]-1-piperidinyl]ethyl]-1,2,3,4-tetrahydro-4-oxo-2-quinazolineacetate (E)-2-butenedioate (1:2); 25 mp. 195.6°C (compound 141).

Example 54

30 A mixture of 3.2 parts of N-[2-[4-[(1-[(4-fluorophenyl)methyl]-1H-benzimidazol-2-yl]amino]-1-piperidinyl]ethyl]-1,2-benzenediamine, 1.25 parts of 1,1'-bis[1H-imidazol-1-yl]methanethione and 45 parts of tetrahydrofuran was stirred overnight at room temperature. The reaction mixture was evaporated and the residue was taken up in 4-methyl-2-pentanone. The organic phase was washed twice with water, 35 dried, filtered and evaporated. The residue was purified by column

-70-

chromatography over silica gel using a mixture of trichloromethane and methanol (90:10 by volume) as eluent. The pure fractions were collected and the eluent was evaporated. The residue was crystallized from acetonitrile, yielding 1.9 parts of 1-[2-[4-[(1-[(4-fluorophenyl)methyl]-1H-benzimidazol-2-yl]amino]-1-piperidinyl]ethyl]-1,3-dihydro-2H-benzimidazole-2-thione; mp. 235.3°C (compound 142).

Example 55

To a stirred mixture of 4.6 parts of N^4 -[2-[4-[(1-[(4-fluorophenyl)methyl]-1H-benzimidazol-2-yl]amino]-1-piperidinyl]ethyl]-4,5-10 pyrimidinediamine, 2.25 parts of N,N -diethylethanamine and 195 parts of dichloromethane were added dropwise 1.75 parts of carbonothioic dichloride. Upon completion, stirring was continued for 3 hours at reflux temperature. The reaction mixture was evaporated. The residue was purified by column chromatography over silica gel using a 15 mixture of trichloromethane and methanol, saturated with ammonia, (95:5 by volume) as eluent. The pure fractions were collected and the eluent was evaporated. The residue was converted into the hydrochloride salt in ethanol and 2-propanol. The salt was filtered off and dried, yielding 1 part (15.4%) of 9-[2-[4-[(1-[(4-fluorophenyl)methyl]-1H-benzimidazol-2-yl]amino]-1-piperidinyl]ethyl]-7,9-20 dihydro-8H-purine-8-thione trihydrochloride dihydrate; mp. 244.7°C (compound 143).

Example 56

7:5 Parts of 6-chloro- N^4 -[2-[4-[(1-[(4-fluorophenyl)methyl]-1H-benzimidazol-2-yl]amino]-1-piperidinyl]ethyl]-4,5-pyrimidinediamine and 3.6 parts of urea were heated together till about 220°C during 10 minutes. The resulting melt was cooled and suspended in water. The solid was filtered off, washed with water and ethanol and recrystallized from a mixture of N,N -dimethylacetamide, ethanol and 30 water, yielding 3.9 parts (49.9%) of 6-chloro-9-[2-[4-[(1-[(4-fluorophenyl)methyl]-1H-benzimidazol-2-yl]amino]-1-piperidinyl]ethyl]-7,9-dihydro-8H-purin-8-one; mp. 266.2°C (compound 144).

In a similar manner there was also prepared:

9-[2-[4-[(1-[(4-fluorophenyl)methyl]-1H-benzimidazol-2-yl)amino]-1-piperidinyl]ethyl]-7,9-dihydro-8H-purin-8-one; mp. 260.5°C;
(compound 145).

5 Example 57

A mixture of 5 parts of ethyl ethanimide hydrochloride, 9 parts of N⁶-[2-[4-[(1-[(4-fluorophenyl)methyl]-1H-benzimidazol-2-yl)amino]-1-piperidinyl]ethyl]-2,3,6-pyridinetriamine and 100 parts of acetic acid was stirred overnight at room temperature. The reaction mixture was evaporated. The residue was dissolved in trichloromethane. Water was added and sodium hydrogen carbonate was added till foaming had ceased. The layers were separated. The organic layer was dried, filtered and evaporated. The residue was purified by column-chromatography over silica gel using a mixture of 15 trichloromethane and methanol, saturated with ammonia, (95:5 by volume) as eluent. The pure fractions were collected and the eluent was evaporated. The residue was crystallized from 2-propanone. The product was filtered off and dried, yielding 4.8 parts (48.5%) of N-[2-[4-[(1-[(4-fluorophenyl)methyl]-1H-benzimidazol-2-yl)amino]-1-piperidinyl]ethyl]-2-methyl-1H-imidazo[4,5-b]pyridin-5-amine; mp. 202.0°C (compound 146).

Example 58

A mixture of 6.5 parts of ethyl 3-bromo-4-oxo-1-piperidine-carboxylate, 8.6 parts of N-[2-[4-[(1-[(4-fluorophenyl)methyl]-1H-benzimidazol-2-yl)amino]-1-piperidinyl]ethyl]thiourea and 80 parts of absolute ethanol was stirred and refluxed overnight. The reaction mixture was evaporated and water was added to the residue. The free base was liberated with a sodium hydroxide solution and extracted with 4-methyl-2-pentanone. The extract was dried, filtered and evaporated. The oily residue was converted into the (E)-2-butenedioate salt in 2-propanone and ethanol. The salt was filtered off and dried, yielding 6.66 parts of ethyl 2-[2-[4-[(1-[(4-fluorophenyl)methyl]-1H-benzimidazol-2-yl)amino]-1-piperidinyl]ethyl]-amino]-4,5-dihydro-thiazolo[4,5-d]pyridine-6(7H)-carboxylate (E)-2-butenedioate (1:2) monohydrate; mp. 183.4°C (compound 147).

Example 59

A mixture of 7 parts of 6-chloro- N^4 -[2-[4-[[1-[(4-fluorophenyl)methyl]-1H-benzimidazol-2-yl]amino]-1-piperidinyl]-ethyl]-4,5-pyrimidinediamine, 2.1 parts of carbon disulfide and 90.5 parts of N,N-dimethylformamide was stirred overnight at 70°C. The reaction mixture was poured into water. The product was extracted with trichloromethane. The extract was dried, filtered and evaporated. The residue was crystallized from ethanol. The product was filtered off and dried in vacuo overnight at 120°C, yielding 2.3 parts (29%) of 7-[[2-[4-[[1-[(4-fluorophenyl)methyl]-1H-benzimidazol-2-yl]amino]-1-piperidinyl]ethyl]amino]-thiazolo[5,4-d]-pyrimidine-2-thiol monohydrochloride; mp. 226.5°C (compound 148).

Example 60

A mixture of 2 parts of 2-thiazolamine, 12.7 parts of 1-bromo-4-[4-[[1-[(4-fluorophenyl)methyl]-1H-benzimidazol-2-yl]amino]-1-piperidinyl]-2-butanone, 6.4 parts of sodium carbonate and 135 parts of methylbenzene was stirred and refluxed for 3 hours using a water separator. The whole was filtered and the filtrate was evaporated. The residue was purified twice by column chromatography over silica gel using a mixture of trichloromethane and methanol, saturated with ammonia, (96:4 by volume) as eluent. The pure fractions were collected and the eluent was evaporated. The residue was crystallized from acetonitrile, yielding 0.5 parts (5.3%) of 1-[(4-fluorophenyl)methyl]-N-[1-[2-(imidazo[2,1-b]thiazol-6-yl)ethyl]-4-piperidinyl]-1H-benzimidazol-2-amine; mp. 222.7°C (compound 149).

In a similar manner there were also prepared:

1-[(4-fluorophenyl)methyl]-N-[1-[2-(imidazo[1,2-a]pyridin-2-yl)ethyl]-4-piperidinyl]-1H-benzimidazol-2-amine; mp. 208.0°C; (comp. 150); and 1-[(4-fluorophenyl)methyl]-N-[1-[2-(imidazo[3,2-a]pyrimidin-2-yl)-ethyl]-4-piperidinyl]-1H-benzimidazol-2-amine; mp. 263.8°C; (compound 151).

Example 61

A mixture of 4 parts of 1-[(4-fluorophenyl)methyl]-N-[1-[(imidazo[1,2-a]pyrazin-2-yl)methyl]-4-piperidinyl]-1H-benzimidazol-2-amine, 50 parts of acetic acid and 80 parts of

methanol was hydrogenated at normal pressure and at 20°C with 2 parts of platinum-on-charcoal catalyst 5%. After the calculated amount of hydrogen was taken up, the catalyst was filtered off and the filtrate was evaporated. The residue was purified by column chromatography over 5 silica gel using a mixture of trichloromethane and methanol, saturated with ammonia, (96:4 by volume) as eluent. The pure fractions were collected and the eluent was evaporated. The residue was converted into the hydrochloride salt in ethanol. The salt was filtered off and dried, yielding 1.5 parts (32%) of 1-[(4-fluorophenyl)methyl]-N-[1-
10 [(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-2-yl)methyl]-4-piperidinyl]-
1H-benzimidazol-2-amine trihydrochloride; mp. 279.7°C (compound 152).

The useful antihistaminic properties of the compounds of formula (I) are demonstrated in the following test procedure.

15

Protection of rats from compound 48/80-induced lethality.

Compound 48/80, a mixture of oligomers obtained by condensation of 4-methoxy-N-methylbenzeneethanamine and formaldehyde has been 20 described as a potent histamine releasing agent (Int. Arch. Allergy, 13, 336 (1958)). The protection from compound 48/80-induced lethal circulatory collapse appears to be a simple way of evaluating 25 quantitatively the antihistaminic activity of test compounds. Male rats of an inbred Wistar strain, weighing 240-260 g were used in the experiment. After overnight starvation the rats were transferred to conditioned laboratories (temp. = 21 \pm 1°C, relative humidity = 65 \pm 5%).

The rats were treated subcutaneously or orally with a test compound or 30 with the solvent (NaCl solution, 0.9%). One hour after treatment there was injected intravenously compound 48/80, freshly dissolved in water, at a dose of 0.5 mg/kg (0.2 ml/100 g of body weight). In control experiments, wherein 250 solvent-treated animals were injected with the standard dose of compound 48/80, not more than 2.8% of the animals survived after 4 hours. Survival after 4 hours is therefore considered 35 to be a safe criterion of a protective effect of drug administration.

The ED_{50} -values of the compounds of formula (I) are listed in the first column of table 1. Said ED_{50} -values are the values in mg/kg body weight at which the tested compounds protect 50% of the tested animals against compound 48/80-induced lethality.

5 The compounds of formula (I) and the pharmaceutically acceptable acid addition salts thereof are also potent serotonin-antagonists. The potency of the subject compounds as serotonin-antagonists is clearly evidenced by the results obtained in the following tests wherein the antagonistic activity of the subject compounds on the 10 effect of serotonin is examined.

Antagonistic activity on the effects of serotonin in the gastric lesion test.

15

A. Lesions induced by compound 48/80:

Compound 48/80 (a mixture of oligomers obtained by condensation of 4-methoxy-N-methylbenzeneethanamine and formaldehyde) is a potent releaser of vasoactive amines from endogenous stores such as, for 20 example, histamine and serotonin. Rats injected with compound 48/80 exhibit consistent changes of blood flow in different vascular beds: cyanosis of the ears and the extremities are prominent within five minutes after injection of the compound; the rats die from shock within 30 minutes. The shock, followed by death, can be avoided if the 25 rats are pretreated with a classical H 1 antagonist.

However the stimulatory effects on gastric secretion are not suppressed so that rats treated with compound 48/80 and protected from shock by an H 1 antagonist may exhibit all signs of intensive 30 gastric gland activity: gross autopsy shows distended stomachs with abnormal contents and rough bright red patches all over the mucosa, corresponding to areas of disintegrated glands. A number of known serotonin-antagonists such as, for example, methysergide, cyproheptadine; cinanserin, mianserin, pipamperone, spiperone, pizotifen and metergoline, prevent completely the cyanosis of ears and 35 extremities as well as the lesions in the glandular area of the

stomach and the abnormal gastric distension.

B. Method:

Male rats of a Wistar inbred strain, weighing 220-250 g, were starved overnight, water being available ad libitum. The test 5 compounds were administered orally as a solution or as a suspension in aqueous medium. A control rat and a "blank" rat received the test compound. One hour later 5-[4-(diphenylmethyl)-1-piperazinyl-methyl]-1-methyl-1H-benzimidazole-2-methanol was administered subcutaneously to all rats at the dose of 2.5 mg/kg. Two hours after 10 the oral or subcutaneous administration of the test compound, the compound 48/80 (freshly solved in water at a concentration of 0.25 mg/ml) was injected intravenously into all rats (dose: 1 mg/kg) except the "blank" rats.

Four hours after the intravenous injection of compound 48/80, the rats 15 were decapitated and the stomachs were removed. Subsequently the stomachs were inspected for distension and contents (blood, fluid, food) and thoroughly rinsed. The macroscopic lesions were scored from 0 to +++, 0 corresponding to complete absence of visible lesions and the highest score corresponding to reddish rough patches covering more 20 than half the glandular area.

The second column of Table 1 shows for a number of compounds of formula (I) the doses (in mg/kg body weight) at which the distension of the stomach as well as the lesions in the glandular area of the stomach are completely absent in 50% of the test rats (ED_{50} -value). 25 The compounds listed in Table 1 are not given for the purpose of limiting the invention thereto but only to exemplify the useful pharmacological activities of all the compounds within the scope of formula (I).

Table 1

	Comp. No.	Column 1	Column 2
		Compound 48/80 lethality test in rats-ED ₅₀ in mg/kg body weight	gastric lesion test ED ₅₀ in mg/kg body weight
5	142	0.16	0.63
	4	0.16	0.31
	109	0.04	0.04
10	147	0.31	0.63
	110	0.16	0.31
	111	0.02	0.08
	112	0.02	0.16
	113	0.04	-
15	114	0.02	0.63
	24	0.08	0.63
	25	0.16	-
	5	0.16	0.04
	22	0.16	-
20	26	0.08	-
	6	0.08	0.63
	7	0.04	0.31
	1	0.31	0.63
	8	0.16	0.63
25	9	0.08	0.16
	10	0.08	0.16
	115	0.02	0.16
	27	0.08	-
	11	0.08	0.04
30	12	0.16	0.31
	28	0.04	0.16
	30	0.16	-
	31	0.04	0.02

Table 1 (cont'd)

	Comp. No.	Column 1	Column 2
		Compound 48/80 lethality test in rats-ED ₅₀ in mg/kg body weight	gastric lesion test ED ₅₀ in mg/kg body weight
5	32	0.04	-
	117	0.02	0.31
	146	0.04	0.08
10	121	0.02	0.02
	122	0.02	0.63
	119	0.04	0.63
	108	0.04	0.16
	34	0.08	0.16
15	35	0.02	-
	13	0.02	0.08
	14	0.02	-
	36	0.16	-
	15	0.16	0.31
20	37	0.16	-
	16	0.16	-
	38	0.04	-
	39	0.16	0.63
	40	0.16	0.16
25	41	0.16	0.63
	42	0.16	-
	43	0.16	-
	44	0.16	-
	45	0.08	-
30	132	0.16	-
	150	0.08	0.63
	17	0.31	0.63
	18	0.08	0.16
	129	0.08	0.31
35	48	0.08	-

Table 1 (cont'd)

	Comp. No.	Column 1	Column 2
		Compound 48/80 lethality test in rats-ED ₅₀ in mg/kg body weight	gastric lesion test ED ₅₀ in mg/kg body weight
5	149	0.08	0.08
	128	0.08	-
	151	0.08	-
	49	0.16	0.63
10	152	0.08	0.63
	94	0.31	0.63
	95	0.16	0.63
	96	0.16	-
	93	0.08	0.16
	144	0.08	-
15	97	0.08	0.04
	143	0.31	0.63
	107	0.16	-
	19	0.08	0.01
	69	0.16	-
20	100	0.16	-
	103	0.16	0.63
	70	0.31	0.63
	102	0.08	-
	68	0.08	-
25	104	0.16	0.31
	74	0.04	0.16
	20	0.04	0.63
	75	0.01	-
	76	0.08	-
30	77	0.16	0.31
	21	0.04	0.63
	79	0.16	-
	52	0.31	1.25

Table 1 (cont'd)

	Comp. No.	Column 1	Column 2
		Compound 48/80 lethality test in rats-ED ₅₀ in mg/kg body weight	gastric lesion test ED ₅₀ in mg/kg body weight
5	54	0.31	-
	55	0.08	0.16
	57	0.16	-
	58	0.04	0.63
	59	0.08	0.31
	61	0.04	0.31
10	62	0.04	0.63
	63	0.08	0.63
	80	0.16	0.63
	64	0.08	0.31
	66	0.16	0.63

20 In view of their antihistaminic and serotonin-antagonistic properties, the compounds of formula (I) and their acid-addition salts are very useful in the treatment of allergic diseases such as, for example, allergic rhinitis, allergic conjunctivitis, chronic urticaria, allergic asthma and the like.

25 In view of their useful pharmacological properties the subject compounds may be formulated into various pharmaceutical forms for administration purposes. To prepare the pharmaceutical compositions of this invention, a pharmaceutically effective amount of the particular compound, in base or acid-addition salt form, as the active ingredient 30 is combined in intimate admixture with a pharmaceutically acceptable carrier, which carrier may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirable in unitary dosage form suitable, preferably, for administration orally, rectally or by parenteral 35 injection. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed, such as,

for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs and solutions; or solid carriers such as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like in the case of 5 powders, pills, capsules and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed.

For parenteral compositions, the carrier will usually comprise sterile 10 water, at least in large part, though other ingredients, for example, to aid solubility, may be included. Injectable solutions, for example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable suspensions may also be prepared in which case appropriate liquid 15 carriers, suspending agents and the like may be employed. Acid addition salts of (I), due to their increased water solubility over the corresponding base form, are obviously more suitable in the preparation of aqueous compositions.

It is especially advantageous to formulate the aforementioned 20 pharmaceutical compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used in the specification and claims herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. 25 Examples of such dosage unit forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, injectable solutions or suspensions, teaspoonfuls, tablespoonfuls and the like, and segregated multiples thereof.

30 The following formulations exemplify typical pharmaceutical compositions in dosage unit form suitable for systemic administration to animal and human subjects in accordance with the present invention. These examples are given to illustrate and not to limit the scope of the present invention.

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"Active ingredient" (A.I.) as used throughout these examples relates to a compound of formula (I), a possible stereochemically isomeric form or pharmaceutically acceptable acid addition salt thereof.

5 Example 62 : ORAL DROPS

500 Grams of the A.I. was dissolved in 0.5 liters of 2-hydroxypropanoic acid and 1.5 liters of the polyethylene glycol at 60-80°C. After cooling to 30-40°C there were added 35 liters of polyethylene glycol and the mixture was stirred well. Then there was added a 10 solution of 1750 grams of sodium saccharin in 2.5 liters of purified water and while stirring there were added 2.5 liters of cocoa flavor and polyethylene glycol q.s. to a volume of 50 liters, providing an oral drop solution comprising 10 milligrams of the A.I. per milliliter. The resulting solution was filled into suitable containers.

15 Example 63 : ORAL SOLUTION

9 Grams of methyl 4-hydroxybenzoate and 1 gram of propyl 4-hydroxybenzoate were dissolved in 4 liters of boiling purified water. In 3 liters of this solution were dissolved first 10 grams of 2,3-dihydroxybutanedioic acid and thereafter 20 grams of the A.I. The 20 latter solution was combined with the remaining part of the former solution and 12 liters 1,2,3-propanetriol and 3 liters of sorbitol 70% solution were added thereto. 40 Grams of sodium saccharin were dissolved in 0.5 liters of water and 2 milliliters of raspberry and 2 milliliters of gooseberry essence were added. The latter solution was 25 combined with the former, water was added q.s. to a volume of 20 liters providing an oral solution comprising 20 milligrams of the active ingredient per teaspoonful (5 milliliters). The resulting solution was filled in suitable containers.

Example 64 : CAPSULES

30 20 Grams of the A.I., 6 grams sodium lauryl sulfate, 56 grams starch, 56 grams lactose, 0.8 grams colloidal silicon dioxide, and 1.2 grams magnesium stearate were vigorously stirred together. The resulting mixture was subsequently filled into 1000 suitable hardened gelating capsules, comprising each 20 milligrams of the active 35 ingredient.

Example 65 : FILM-COATED TABLETSPreparation of tablet core

A mixture of 100 grams of the A.I., 570 grams lactose and 200 grams starch was mixed well and thereafter humidified with a solution of 5 grams sodium dodecyl sulfate and 10 grams polyvinylpyrrolidone in about 200 milliliters of water. The wet powder mixture was sieved, dried and sieved again. Then there was added 100 grams microcrystalline cellulose and 15 grams hydrogenated vegetable oil. The whole was mixed well and compressed into tablets, giving 10.000 tablets, each 10 containing 10 milligrams of the active ingredient.

Coating

To a solution of 10 grams methyl cellulose in 75 milliliters of denatured ethanol there was added a solution of 5 grams of ethyl cellulose in 150 milliliters of dichloromethane. Then there were added 15 75 milliliters of dichloromethane and 2.5 milliliters 1,2,3-propanetriol. 10 Grams of polyethylene glycol was molten and dissolved in 75 milliliters of dichloromethane. The latter solution was added to the former and then there were added 2.5 grams of magnesium octadecanoate, 5 grams of polyvinylpyrrolidone and 30 milliliters of concentrated 20 colour suspension (Opaspray K-1-2109) and the whole was homogenated.

The tablet cores were coated with the thus obtained mixture in a coating apparatus.

Example 66 : INJECTABLE SOLUTION

1.8 Grams methyl 4-hydroxybenzoate and 0.2 grams propyl 4-hydroxybenzoate were dissolved in about 0.5 liters of boiling water for injection. After cooling to about 50°C there were added while stirring 4 grams lactic acid, 0.05 propylene glycol and 4 grams of the A.I.. The solution was cooled to room temperature and supplemented with water for injection q.s. ad 1 liter volume, giving a solution of 4 30 milligrams A.I. per milliliters. The solution was sterilized by filtration (U.S.P. XVII p. 811) and filled in sterile containers.

Example 67 : SUPPOSITORIES

3 Grams A.I. was dissolved in a solution of 3 grams 2,3-dihydroxybutanedioic acid in 25 milliliters polyethylene glycol 400. 12 Grams 35 surfactant and triglycerides q.s. ad 300 grams were molten together.

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The latter mixture was mixed well with the former solution. The thus obtained mixture was poured onto moulds at a temperature of 37-38°C to form 100 suppositories each containing 30 milligrams of the active ingredient.

5

The present invention is also related with a method of treating allergic diseases in warm-blooded animals suffering from said allergic diseases by administering an effective anti-allergic amount of a compound of formula (I) or a pharmaceutically acceptable acid addition salt thereof.

Suitable doses administered daily to subjects are varying from 0.1 to 100 mg, more preferably from 1 to 50 mg.

15

20

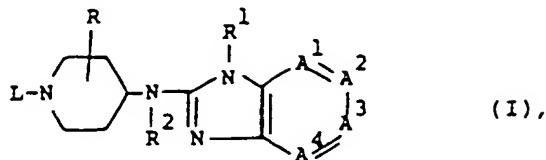
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CLAIMS

1 1. A chemical compound having the formula



2 a pharmaceutically acceptable acid addition salt or a
3 possible stereochemically isomeric form thereof, wherein:

4 $\text{A}^1=\text{A}^2=\text{A}^3=\text{A}^4$ is a bivalent radical having the formula

5 $-\text{CH}=\text{CH}-\text{CH}=\text{CH}-$ (a),

6 $-\text{N}=\text{CH}-\text{CH}=\text{CH}-$ (b),

7 $-\text{CH}=\text{N}-\text{CH}=\text{CH}-$ (c),

8 $-\text{CH}=\text{CH}-\text{N}=\text{CH}-$ (d), or

9 $-\text{CH}=\text{CH}-\text{CH}=\text{N}-$ (e),

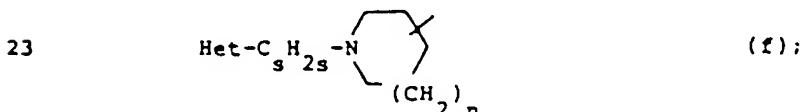
10 wherein one or two hydrogen atoms in said radicals (a) - (e) may,
11 each independently from each other, be replaced by halo, lower
12 alkyl, lower alkyloxy, trifluoromethyl or hydroxy;

13 R is a member selected from the group consisting of hydrogen and
14 lower alkyl;

15 R¹ is a member selected from the group consisting of hydrogen,
16 alkyl, cycloalkyl, Ar¹ and lower alkyl substituted with one or two
17 Ar¹ radicals;

18 R² is a member selected from the group consisting of hydrogen,
19 lower alkyl, cycloalkyl, (lower alkyl)-CO-, lower alkyl-O-(CO)- and
20 Ar²-lower alkyl;

21 L is a member selected from the group consisting of
22 a radical of formula



24 a radical of formula

25 $\text{Het}-\text{C}_{\text{s}}^{\text{H}}\text{H}_{2\text{s}}-\text{Y}-\text{Alk}-$

(g); and

26 a radical of formula

27 $\text{Het}-\text{C}_{\text{s}}^{\text{H}}\text{H}_{2\text{s}}-\text{Z}-\overset{\text{X}}{\underset{\text{Y}}{\text{C}}}-\text{Y}-\text{Alk}-$ (h),

28 wherein n is 0 or the integer 1 or 2;

29 s is 0 or an integer of from 1 to 6 inclusive;

30 Alk is lower alkanediyl;

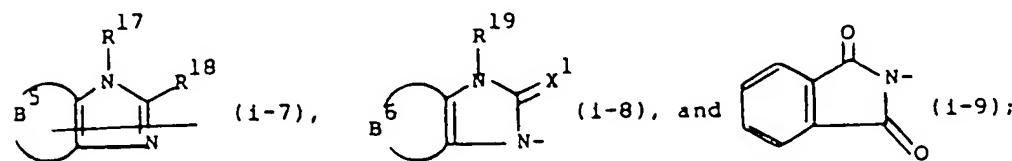
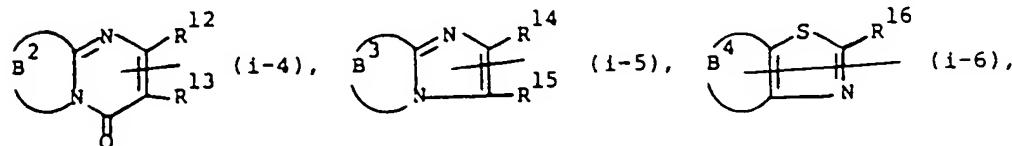
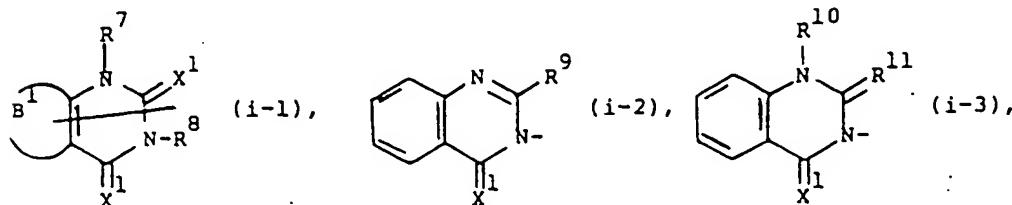
31 Y is O, S, NR^3 or a direct bond;32 X is O, S, $\text{CH}-\text{NO}_2$ or NR^4 ;33 Z is O, S, NR^5 or a direct bond; and34 Het is an optionally substituted five- or six-membered heterocyclic
35 ring containing at least one nitrogen atom and being condensed with
36 an optionally substituted five- or six-membered ring, provided that:

- 37 i) when Het is connected to $\text{C}_{\text{s}}^{\text{H}}\text{H}_{2\text{s}}$ on a carbon atom then
38 said five- or six-membered ring is not condensed with an
39 optionally substituted benzene ring;
- 40 ii) when L is a radical either of formula (f), or of formula
41 (g) wherein Y is other than a direct bond, or of formula
42 (h) wherein Z is other than a direct bond, wherein in said
43 radicals (f), (g) or (h) Het is connected to $\text{C}_{\text{s}}^{\text{H}}\text{H}_{2\text{s}}$ on
44 a nitrogen atom then s is not 0;
- 45 iii) when $\text{A}^1=\text{A}^2-\text{A}^3=\text{A}^4$ is a radical of formula (a) or
46 (b) and L is a radical of formula (g) wherein s is 0 and
47 Y is a direct bond then Het is other than a 2,3-dihydro-
48 2-oxo-1H-benzimidazol-1-yl or a 2,3-dihydro-3-oxo-
49 benzoxazin-4-yl radical;

50 said R^3 being hydrogen, lower alkyl, (Ar^2) lower alkyl, 2-lower
51 alkyloxy-1,2-dioxoethyl or a radical of formula $-\text{C}(-\text{X})-\text{R}^6$, R^6
52 being hydrogen, lower alkyl, Ar^2 , Ar^2 -lower alkyl, lower alkyloxy,
53 Ar^2 -lower alkyloxy, mono- or di(lower alkyl)amino, Ar^2 -amino,
54 Ar^2 -lower alkylamino or Ar^2 -lower alkyl(lower alkyl)amino;
55 said R^4 being hydrogen, lower alkyl, cyano, nitro, Ar^2 -sulfonyl,

56 lower alkylsulfonyl, lower alkylcarbonyl or Ar^2 -carbonyl; and
 57 said R^5 being hydrogen or lower alkyl;
 58 wherein Ar^1 is a member selected from the group consisting of
 59 phenyl, being optionally substituted with up to three substituents
 60 each independently selected from the group consisting of halo,
 61 hydroxy, nitro, cyano, trifluoromethyl, lower alkyl, lower alkyloxy,
 62 lower alkylthio, mercapto, amino, mono- and di(lower alkyl)amino,
 63 carboxyl, lower alkyloxycarbonyl and lower alkyl-CO-; thienyl;
 64 pyrazinyl; thiazolyl and imidazolyl optionally substituted by lower
 65 alkyl; and wherein Ar^2 is a member selected from the group
 66 consisting of phenyl being optionally substituted with up to three
 67 substituents each independently selected from the group consisting
 68 of halo, hydroxy, nitro, cyano, trifluoromethyl, lower alkyl,
 69 lower alkyloxy, lower alkylthio, mercapto, amino, mono- and di(lower
 70 alkyl)amino, carboxyl, lower alkyloxycarbonyl and (lower alkyl)-CO.
 71

1 2. A chemical compound according to claim 1, wherein Het is a
 2 member of the group consisting of



3 wherein each X^1 is independently O or S;
4 R^7 , R^8 , R^{10} , R^{17} and R^{19} are each independently hydrogen, lower alkyl,
5 Ar^2 -lower alkyl, hydroxylower alkyl or lower alkyloxycarbonyl;
6 R^9 , R^{11} , R^{12} , R^{13} , R^{14} , R^{15} , R^{16} and R^{18} are each independently
7 hydrogen, lower alkyl, hydroxy, mercapto, lower alkyloxy, lower
8 alkylthio, halo and (lower alkyloxycarbonyl)lower alkyl;
9 B^1 is $-CH=CH-CH=CH-$, $-S-CH=CH-$ or $-N=CH-NH-$;
10 B^2 is $-CH=CH-CH=CH-$, $-S-(CH_2)_2$, $-S-(CH_2)_3$ or $-(CH_2)_4$;
11 B^3 is $-CH=CH-CH=CH-$, $-N=CH-CH=CH-$, $-CH=N-CH=CH-$, $-CH_2-NH-(CH_2)_2-$ or
12 $-S-CH=CH-$;
13 B^4 is $-CH_2-NH-(CH_2)_2-$, $-N=CH-CH=CH-$ or $-N=CH-N=CH-$;
14 B^5 is $-N=CH-CH=CH-$, $-CH=N-CH=CH-$ or $-CH=N-CH=N-$;
15 B^6 is $-CH=CH-CH=CH-$ or $-CH=N-CH=N-$;
16 wherein one or two hydrogen atoms in said radicals B^1 , B^2 , B^3 , B^4 ,
17 B^5 or B^6 or in the benzene part of the radicals of formula (i-2),
18 (i-3) or (i-9) may be replaced by lower alkyl, lower alkylthio, lower
19 alkyloxy or halo where said hydrogen atom is bonded on a carbon atom,
20 or by lower alkyl, lower alkyloxycarbonyl, Ar^2 -lower alkyl, where
21 said hydrogen is bonded on a nitrogen atom.
22 It is clear that R^7 , R^8 , R^{12} , R^{13} , R^{14} , R^{15} , R^{16} , R^{17} or R^{18} is absent
23 where the radical of formula (i-1), respectively (i-4), (i-5), (i-6)
24 and (i-7) is connected to C_sH_{2s} on the atom bearing R^7 , R^8 , R^{12} , R^{13} ,
25 R^{14} , R^{15} , R^{16} , R^{17} or R^{18} .

1 3. A chemical compound according to claim 2 wherein L is a
2 radical of formula (g) or (h).

1 4. A chemical compound selected from the group consisting of
2 3-[2-[4-[(3-(2-furanyl methyl)-3H-imidazo[4,5-b]pyridin-2-yl)amino]-
3 1-piperidinyl]ethyl]-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one and the
4 pharmaceutically acceptable acid addition salts thereof.

1 5. A pharmaceutical composition comprising a suitable pharmaceutical
2 carrier and as an active ingredient a therapeutically effective amount
3 of a compound as claimed in any one of claims 1 to 4.

1 6. An anti-allergic pharmaceutical composition comprising a
2 suitable pharmaceutical carrier and as an active ingredient an
3 effective anti-allergic amount of a compound as claimed in any one of
4 claims 1 to 4.

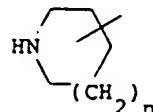
1 7. A method of preparing a pharmaceutical composition,
 2 characterized in that a therapeutically effective amount of a compound
 3 as claimed in any one of claims 1 to 4 is intimately mixed with
 4 suitable pharmaceutical carriers.

1 8. A compound as claimed in any one of claims 1 to 4 for use as
 2 a medicine.

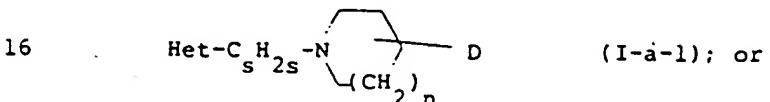
1 9. A compound as claimed in any one of claims 1 to 4 for use as
 2 an anti-allergic medicine.

1 10. A process for preparing a chemical compound as claimed in
 2 claim 1, characterized by

3 a) alkylating a piperidine of formula Q^2 -D (III) with an intermediate
 4 of formula Het- Q^1 (II) in a reaction-inert solvent wherein
 5 1) Q^2 is hydrogen and Q^1 , combined with Het, forms a radical of
 6 formula L-W (II-a), said W representing an appropriate reactive
 7 leaving group such as, for example, halo, e.g., chloro, bromo or
 8 iodo, or a sulfonyloxy group, e.g. methylsulfonyloxy or 4-methyl-
 9 phenylsulfonyloxy; or
 10 2) Q^1 is a radical of formula $-C_sH_{2s}-W^1$, said W^1 having the
 11 previously defined meaning of W provided that, where s is 0, W^1 may
 12 also represent a lower alkyloxy or lower alkylthio group, and Q^{2a}
 13 is a radical of formula



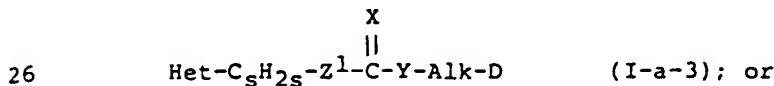
15 thus preparing a compound of formula



17 3) Q^1 is a radical of formula $-C_sH_{2s}-W^1$ and Q^{2a} is a radical
 18 of formula HY¹-Alk-, said Y¹ having the previously defined
 19 meaning of Y provided that Y is other than a direct bond, thus
 20 preparing a compound of formula



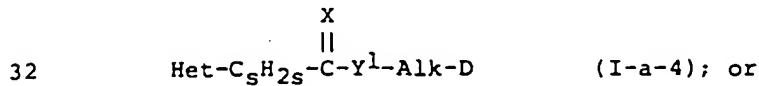
22 4) Q^1 is a radical of formula $-C_sH_{2s}-W^1$ and Q^{2a} is a radical
 23 of formula $HZ^1-C(X)-Y-Alk-$, said Z^1 having the previously
 24 defined meaning of Z provided that Z is other than a direct
 25 bond, thus preparing a compound of formula



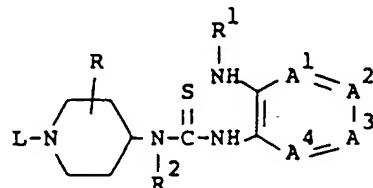
27 5) Q^1 is a radical of formula $-C_sH_{2s}-Y^1H$ and Q^2 is a
 28 radical of formula $W-Alk-$, thus preparing a compound of formula



30 6) Q^1 is a radical of formula $-C_sH_{2s}-Z-C(X)-Y^1H$ and Q^2 is a
 31 radical of formula $W-Alk$, thus preparing a compound of formula



33 b) cyclodesulfurizing an intermediate of formula



(IV)

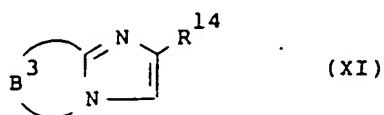
34 with an appropriate alkyl halide, metal oxide or metal salt in a
 35 reaction-inert solvent; or

36 c) reacting an intermediate of formula $\text{Het}-C_sH_{2s}-Z^1H$ (V) with a
 37 piperidine of formula $X^1=C=N-Alk-D$ (VI) in a suitable reaction-
 38 inert solvent, thus preparing a compound of formula

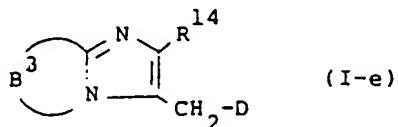
39 $\text{Het}-C_sH_{2s}-Z^1-C(X^1)-NH-Alk-D$ (I-b-1); or

40 d) reacting an intermediate of formula $\text{Het}-C_sH_{2s}-N=C=X^1$ (VII), said X^1
 41 being O or S, with a piperidine of formula $HY^1-Alk-D$ (VIII) in a
 42 suitable reaction-inert solvent, thus preparing a compound of formula
 43 $\text{Het}-C_sH_{2s}-NH-C(X^1)-Y^1-Alk-D$ (I-b-2); or

44 e) reacting an intermediate of formula $\text{Het-C}_{\text{s}2\text{s}}^{\text{1}}-\text{C}(\text{X}^1)-\text{OH}$ (IX) with a
 45 piperidine of formula $\text{HY}^1\text{-Alk-D}$ (VIII) in a suitable reaction-inert
 46 solvent, if desired, after converting the OH-function in (VIII) in a
 47 suitable leaving group, or, if desired, by reacting (IX) with (VIII)
 48 together with an appropriate reagent capable of forming amides or
 49 esters; thus preparing $\text{Het-C}_{\text{s}2\text{s}}^{\text{1}}-\text{C}(\text{X}^1)-\text{Y}^1\text{-Alk-D}$ (I-c); or
 50 f) reacting a piperidine of formula HD (III-a) with a reagent of formula
 51 Het-lower alkenediyl-H (X) in a suitable reaction-inert solvent, thus
 52 preparing a compound of formula Het-Alk-D (I-d); or
 53 g) reacting an intermediate of formula HD (III-a) with a reagent of
 54 formula

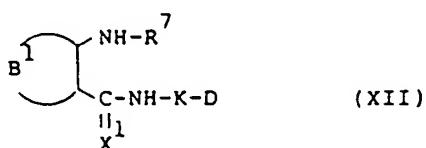


55 in the presence of formaldehyde or a polymeric form thereof
 56 in a suitable solvent, thus preparing a compound of formula

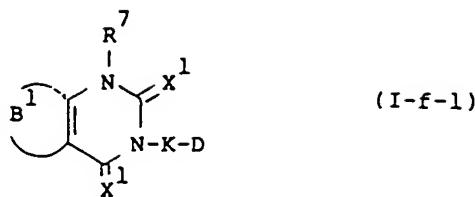


57 wherein B^3 is $-\text{CH}=\text{CH}-\text{CH}=\text{CH}-$, $-\text{CH}=\text{N}-\text{CH}=\text{CH}-$, $-\text{CH}_2-\text{NH}-(\text{CH}_2)_2-$,
 58 $-\text{S}-\text{CH}=\text{CH}-$ or $-\text{N}=\text{CH}-\text{CH}=\text{CH}-$; and R^14 is independently selected from the
 59 group consisting of hydrogen, lower alkyl, hydroxy, mercapto, lower
 60 alkyloxy, lower alkylthio, halo and (lower alkyloxycarbonyl)-
 61 lower alkyl; or

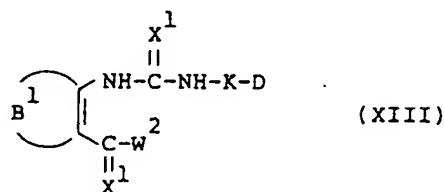
62 h) reacting an intermediate of formula



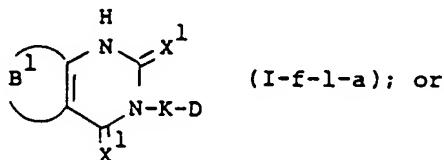
63 with a $\text{C}=\text{X}^1$ generating agent in a reaction-inert solvent thus
 64 preparing a compound of formula



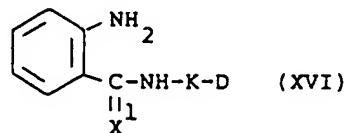
65 wherein B^1 is $-\text{CH}=\text{CH}-\text{CH}=\text{CH}-$, $-\text{S}-\text{CH}=\text{CH}-$ or $-\text{N}=\text{CH}-\text{NH}-$; and R^7 is
66 selected from the group consisting of hydrogen, lower alkyl,
67 Ar^2 -lower alkyl, hydroxylower alkyl or lower alkyloxycarbonyl; or
68 i) cyclizing an intermediate of formula



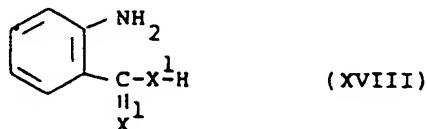
69 wherein W^2 is an appropriate reactive leaving group, in a
70 reaction-inert solvent and, if desired, in the presence of an
71 appropriate base, thus preparing a compound of formula



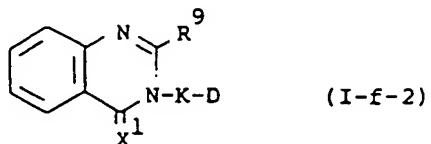
72 j) cyclizing the intermediate of formula



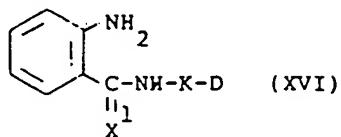
73 with an acid of formula R^9COOH (XVII) or a functional derivative
74 thereof; or cyclizing an intermediate of formula



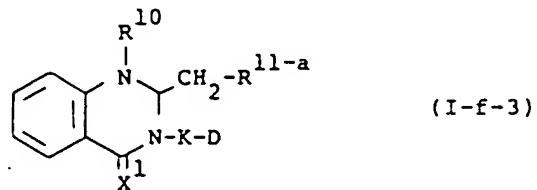
75 with an aromatic amino acid or -thioacid of the formula
 76 $R^9C(O)-NH-K-D$ (XIX) in a suitable reaction-inert solvent,
 77 thus preparing a compound of formula



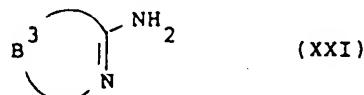
78 wherein R^9 is selected from the group consisting of hydrogen,
 79 lower alkyl, hydroxy, mercapto, lower alkyloxy, lower alkylthio,
 80 halo and (lower alkyloxycarbonyl)lower alkyl; or
 81 k) reacting an intermediate of formula



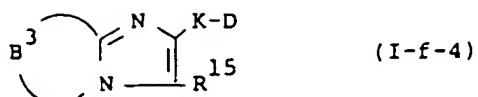
82 with an acetylene derivative of formula $CH \equiv C-R^{11-a}$ (XX) in a
 83 suitable solvent, thus preparing a compound of formula



84 wherein R^{10} is selected from the group consisting of hydrogen,
 85 lower alkyl, Ar^2 -lower alkyl, hydroxylower alkyl or lower
 86 alkyloxycarbonyl; and R^{11-a} is (C_{1-5}) alkyl or (lower alkyloxy-
 87 carbonyl) (C_{1-5}) alkyl; or
 88 1) reacting a reagent of formula



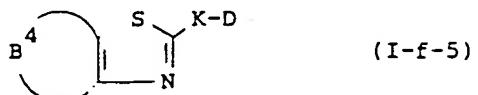
89 with an intermediate of formula $W-CH(R^{15})-C(O)-K-D$ (XXII) in a
 90 suitable reaction-inert solvent thus preparing a compound of formula



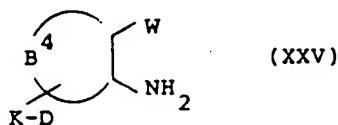
91 wherein R¹⁵ is selected from the group consisting of hydrogen,
 92 lower alkyl, hydroxy, mercapto, lower alkyloxy, lower alkylthio,
 93 halo and (lower alkyloxycarbonyl)lower alkyl; or
 94 m) cyclizing a reagent of formula



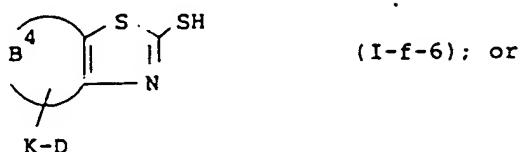
95 with an intermediate of formula H₂NC(S)-K-D (XXIV) in a suitable
 96 reaction-inert solvent thus preparing a compound of formula



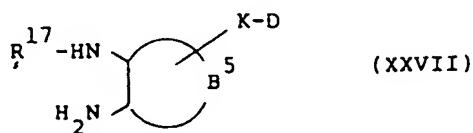
97 wherein B⁴ is -CH₂-NH-(CH₂)₂-, -N=CH-CH=CH- or -N=CH-N=CH-; or
 98 n) cyclizing a reagent of formula



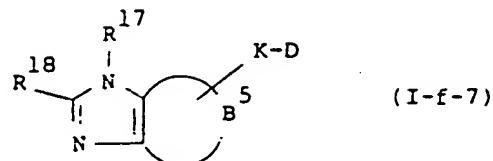
99 with CS₂ in a suitable reaction-inert solvent thus preparing a
 100 compound of formula



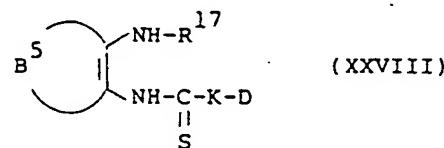
101 o) reacting a reagent of formula R¹⁸-C(NH)-W² (XXVI) with an
 102 intermediate of formula



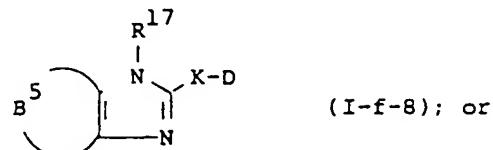
103 in a suitable reaction-inert solvent thus preparing a compound
104 of formula



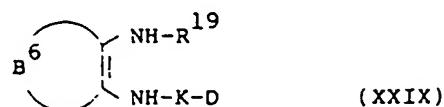
106 wherein B^5 is $-N=CH-CH=CH-$, $-CH=CH-N=CH-$ or $-CH=N-CH=N-$; R^{17} is
107 selected from the group consisting of hydrogen, lower alkyl,
108 Ar^2 -lower alkyl, hydroxylower alkyl or lower alkyloxycarbonyl;
109 and R^{18} is selected from the group consisting of hydrogen,
110 lower alkyl, hydroxy, mercapto, lower alkyloxy, lower
111 alkylthio, halo and (lower alkyloxycarbonyl)lower alkyl; or
112 p) cyclodesulfurizing an intermediate of formula



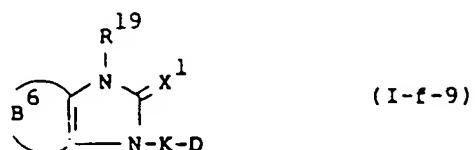
113 with an appropriate alkyl halide, metal oxide or metal salt in a
114 reaction-inert solvent; thus preparing a compound of formula



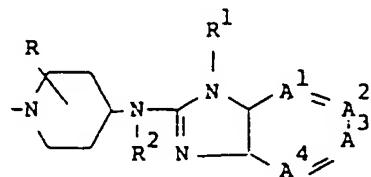
115 q) reacting an intermediate of formula



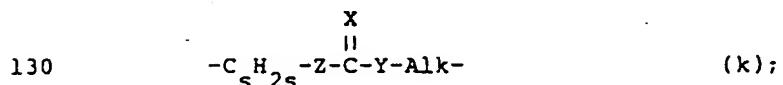
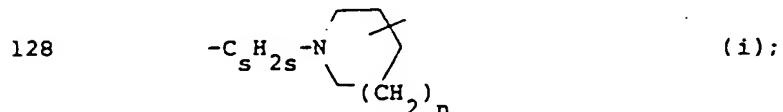
116 with a $C=X^1$ generating agent in a reaction-inert solvent thus
117 preparing a compound of formula



118 wherein B^6 is $-\text{CH}=\text{CH}-\text{CH}=\text{CH}-$ or $-\text{CH}=\text{N}-\text{CH}=\text{N}-$; and R^{19} is selected
 119 from the group consisting of hydrogen, lower alkyl, Ar^2 -lower
 120 alkyl, hydroxylower alkyl or lower alkyloxycarbonyl; or
 121 r) reducing an intermediate of formula $\text{Het}-\text{C}_{s\ 2s}^{\text{H}}-\text{Y}-\text{Alk}'-\text{C}(\text{O})-\text{D}$ (XXX)
 122 with a complex metal hydride in a suitable solvent, thus preparing a
 123 compound of formula $\text{Het}-\text{C}_{s\ 2s}^{\text{H}}-\text{Y}-\text{Alk}'-\text{CH}_2-\text{D}$ (I-g) wherein Alk' has the
 124 previously defined meaning of Alk , provided that one methylene
 125 function is missing;
 126 wherein D represents a radical of formula



127 and K represents a bivalent radical of formula



131 optionally converting the compounds of formula (I) into each other
 132 following art-known functional group transformation procedures; and,
 133 if desired, converting the compounds of formula (I) into a
 134 therapeutically active non-toxic acid-addition salt form by treatment
 135 with an appropriate acid or, conversely, converting the acid-addition
 136 salt into the free base form with alkali; and/or preparing
 137 stereochemically isomeric forms thereof.



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12

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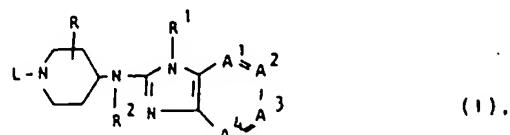
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(54) Bicyclic heterocycl containing N-(bicyclic heterocycl)-4-piperidinamines.

(57) Novel *N*-heterocyclic-4-piperidinamines of the formula



wherein L contains an optionally substituted five- or six-membered ring containing at least one nitrogen atom, and which is condensed with an optionally substituted five- or six-membered ring; the pharmaceutically acceptable acid addition salts and possible stereochemically isomeric forms thereof, which compounds are anti-allergic agents; pharmaceutical compositions containing such compounds as an active ingredient and methods of preparing said compounds and pharmaceutical compositions.

EP 0 144 101 A3



EP 84 20 1611

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
D, A	US-A-4 219 559 (F. JANSSENS et al) -----		C 07 D 401/12 401/14 405/12 405/14 409/12 409/14 417/14 471/04 487/04 513/04 519/00 A 61 K 31/415
The present search report has been drawn up for all claims			TECHNICAL FIELDS SEARCHED (Int. Cl.4)
C 07 D 401/00 405/00 409/00 417/00 471/00 487/00 513/00 519/00 A 61 K 31/00			
<p>Place of search Date of completion of the search</p> <p>THE HAGUE 06-02-1985</p>			Examiner DE BUYSER I.
<p>CATEGORY OF CITED DOCUMENTS</p> <p>X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document</p> <p>T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document</p>			